Readily Accessible sp^3-Rich Cyclic Hydrazine Frameworks Exploiting Nitrogen Fluxionality

By

Conor Luke Dean

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry

Department of Chemistry, University of Warwick

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Declaration

Except where clearly indicated, the work reported in this thesis is an account of my own independent research at the University of Warwick, carried out between October 2016 and March 2020.

The research reported in this thesis has not been submitted, either wholly or in part, for a degree at another institution.

At the time of submission, part of this work has appeared in the scientific literature:

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Abstract

This thesis describes work on the asymmetric synthesis of orthogonally protected cyclic hydrazines, their subsequent functionalization and the study of their structure, to examine their potential as drug-like scaffolds.

Chapter 1 is an introduction to cyclic hydrazines, including a discussion of their relevance to medicinal chemistry as sp^3-rich scaffolds. It includes a summary of previous synthetic methodologies that have been developed to access cyclic hydrazines.

Chapter 2 describes the synthesis of orthogonally protected cyclic hydrazines. Initially a synthetic methodology is developed for the synthesis of orthogonally protected diazetidines. The first method explored ring opening of epoxides with hydrazine nucleophiles. The second, more general method, is based on the Asymmetric Transfer Hydrogenation of aryl ketones, which was successful across a range of ring sizes and substitution patterns. Twenty-eight examples were synthesised, including 4- to 7-membered rings in up to 99% ee.

Chapter 3 is focused on the deprotection and subsequent functionalization of these cyclic hydrazine scaffolds. Initially the functionalisation of pyrazolidines was explored, and suitable conditions for Buchwald-Hartwig couplings were developed using high throughput screening. Derivatisation was subsequently expanded to include acylation and reductive amination reactions and was also shown to be effective across all the ring sizes synthesised in chapter 2.

Chapter 4 describes the study of the 3D structure of the cyclic hydrazine scaffolds. XRD, PMI plots and NMR indicated a preference for the *anti*, *anti* conformation in the solid state and in solution. VT NMR was used to determine if interconversion to other conformational isomers was possible through *N*-inversion, analysis of one system provided evidence this was possible.

Chapter 5 details possible future directions for this work and chapter 6 contains the experimental procedures and characterisation for the novel compounds synthesised in chapters 2 and 3.

Abbreviations

3D	3-Dimensional
acac	Acetylacetone
Ac	Acetate
Ad	Adamantyl
Anthr	Anthracene
Aq	Aqueous
Ar	Aryl
ATH	Asymmetric
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	Broad
Bu	Butyl
cal	Calories
Calcd.	Calculated
Cbz	Carboxybenzyl
CCD	Charge Coupled Device
CM	Complex Mixture
Conv.	Conversion
COSY	Correlated Spectroscopy
Cy	Cyclohexyl
δ	Chemical shift
d	Day(s) or doublet
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DABCO	1,2-Diazabicyclo[2.2.2]octane
DBAD	Dibenzyl azodicarboxylate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
dba	Dibenzylacetone
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DFT	Density Functional Theory
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	Dimethylaminopyridine
DMF	*N*,*N*'-Dimethylformamide
DMSO	Dimethyl sulphoxide
dppf	1,1′-Ferrocenediyl-bis(diphenylphosphine)
dippf	1,1′-Bis(diisopropylphosphino)ferrocene
dr	Diastereomeric ratio
DSC	Differential Scanning Calorimetry
D*t*BAD	Di-tert-butyl azodicarboxylate
ee	Enantiomeric excess
equiv	Equivalents

EP	Explosive Propagation
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron withdrawing group
FT-IR	Fourier Transform-Infrared
g	gram(s)
GC-MS	Gas Chromatography-Mass Spectrometry
h	Hour(s)
HMBC	Heteronuclear Multiple Bond Correlation
HRMS	High Resolution Mass-Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
HPLC	High-Performance Liquid Chromatography
HSAB	Hard-Soft Acids and Bases
Hz	Hertz
*i*Pr	Isopropyl
IPA	Isopropyl Alcohol
IR	Infrared
J	Joules
J	Coupling constant
K	Kelvin
LC-MS	Liquid Chromatography-Mass Spectrometry
LDA	Lithium Diisopropylamide
LLAMA	Lead-Likeness and Molecular Analysis
log	logarithm
M.p.	Melting point
M	Molarity concentration
m	Multiplet
Me	Methyl
Mes	Mesitylene
mg	Milligrams
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mmol	Millimolar
MS	Mass Spectrometry
Ms	Methanesulphonyl
m/z	Mass/charge ratio
*n*Bu	Normal butyl
ng	nanogram(s)
NHC	N-heterocyclic carbene
nm	nanometres
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
NR	No Reaction
Ns	*para*-nitrosulphonyl
P	Pressure or Product

p-	*para*-
p-NBA	*para*-Nitrobenzoic acid
pg	Protecting group
Ph	Phenyl
phth	Phthalimide
pKa	Acid Dissociation constant
PMI	Principle Moment of Inertia
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulphonate
Pyr.	Pyridine
q	Quartet
quin	Quintet
rac	Racemic
Ret	Retention time
R_f	Retention factor
ROESY	Rotating frame Overhauser Enhancement Spectroscopy
rt	Room temperature
s	Singlet
Salen	*N*,*N*'-Ethylenebis(salicylimine)
sBu	*sec*-Butyl
SM	Starting Material
S_NAr	Nucleophilic aromatic substitution
T	Temperature
t	Time
TBAI	Tetrabutylammonium iodide
TBME	*tert*-Butylmethyl ether
TBS	*tert*-Butyldimethylsilyl
*t*Bu	*tert*-Butyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
t_R	Retention time
Ts	*para*-Toluenesulfonyl
wt	Weight
UV	Ultraviolet
VT	Variable Temperature
XRD	X-Ray Diffraction

Chapter 1: Introduction

1.1 Sp^3-Rich Frameworks in Medicinal Chemistry

Over the last decade there has been increasing interest in the synthesis and study of new and more diverse scaffolds for drug discovery programmes. This has been fuelled by increasing interest in 'molecular complexity' and how this fits into the success of candidate molecules within high throughput screening – the pre-eminent method for developing new small molecule drug candidates.[1] The idea is that more complex molecules, which are generally defined as those with a high percentage of sp^3 carbon centres (measured as Fsp^3) are likely to be more topologically complex, which means they possess a more complex 3D structure. They also often contain more chiral centres, which has been found to correlate with higher success in drug discovery programmes. Analysis shows that the mean fraction of sp^3 centres increases as one progresses further through the drug discovery pipeline (Figure 1.1).

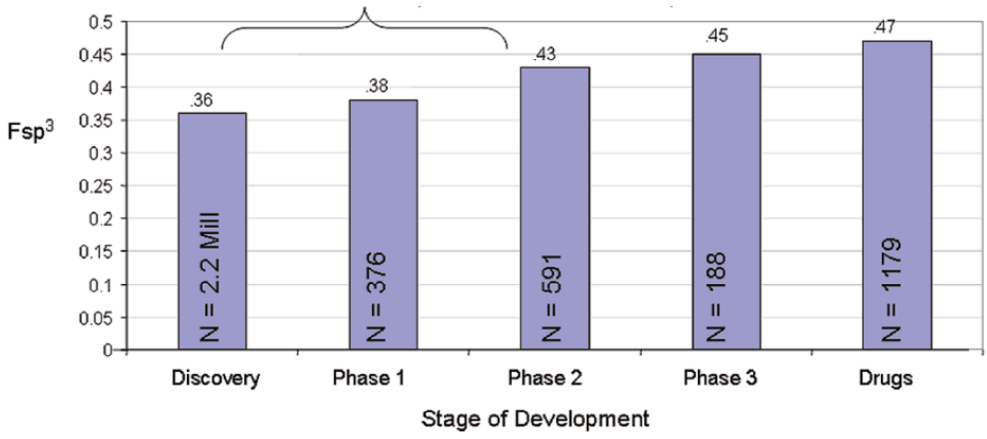


Figure 1.1 Fraction of sp^3 carbon atoms in drug candidates at each stage of development, analysis conducted in 2009 by Lovering *et al.*[1]

In addition to the focus on Fsp^3, other methods of measuring molecular complexity have also been used, including the use of PMI (Principal Moments of Inertia) plots.[2] This uses relatively simple computational processes to calculate the 3D shape of a molecule, and it generates a simple scatter plot that can be used on sample sizes of over 1 million molecules (Figure 1.2). Analysis of small molecule drugs currently on the market (N = 1,045,172) revealed a lack of diversity in shape among these compounds, with almost all of them clustered

on the left hand axis.[3] This means that the majority of the molecules analysed are flat in shape, with rod and disc like shapes dominant, with almost none possessing even moderately spherical character.

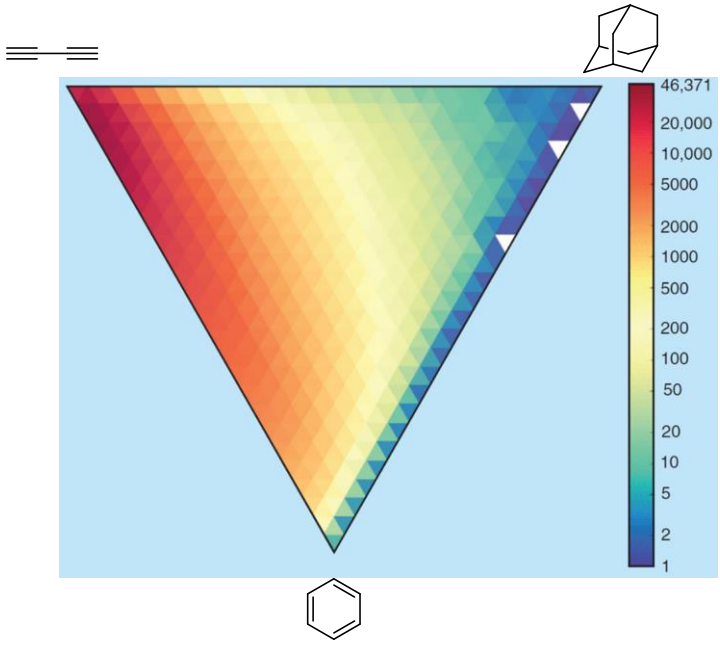


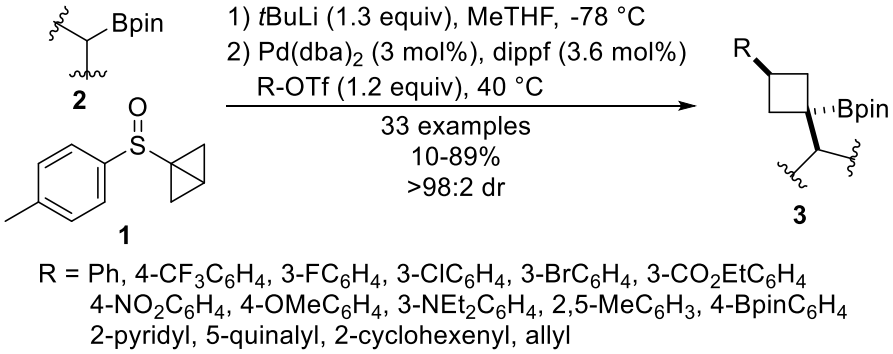
Figure 1.2 PMI plot of over 1 million small molecule drugs, showing their lack of shape diversity, plot by Brown and co-workers.[3]

This general lack of shape diversity is somewhat unsurprising given the most commonly used reactions to synthesise drug candidates. This was shown by analysis from Jordan and Roughley of the reactions used by GlaxoSmithKline, AstraZeneca and Pfizer to make 3566 published compounds in 139 papers.[4] This showed that the most used reactions included acylation processes (22.4% of total), C-C sp^2 couplings (11.5% of total) and N-Ar couplings (6.3% of total) all of which often add flat and rigid functional groups.

1.2 Synthesis of sp^3-Rich Frameworks

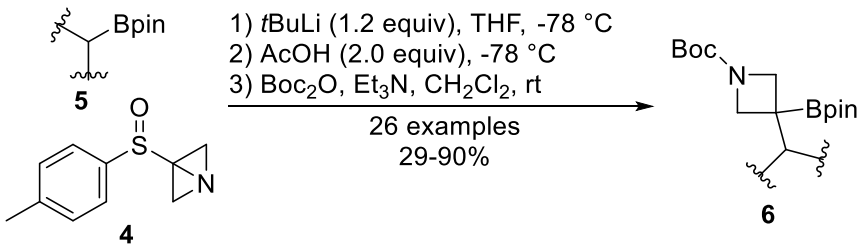
There has been significant recent interest in synthetic methods that can access sp^3-rich frameworks, with a number of elegant strategies reported. Generally, most strategies have involved the synthesis of saturated cyclic frameworks as these structural motifs can often be made enantioselectively and are also more likely to be bioactive. They also offer multiple points for diversification, allowing a wide variety of functionalisation reactions to be employed.

Aggarwal *et al.* have demonstrated that strain release chemistry is a highly efficient way to generate functionalised cyclic systems. They reported a palladium catalysed sigma bond cleavage of the bicyclo[1.1.0]butane boronic ester, which was generated *in situ* from sulphoxide **1**.[5] This reaction was shown to be compatible with wide range of boronic esters and aryl triflate coupling partners, which were combined to give thirty-three different sp^3-rich cyclobutane frameworks diastereoselectively (Scheme 1.1).



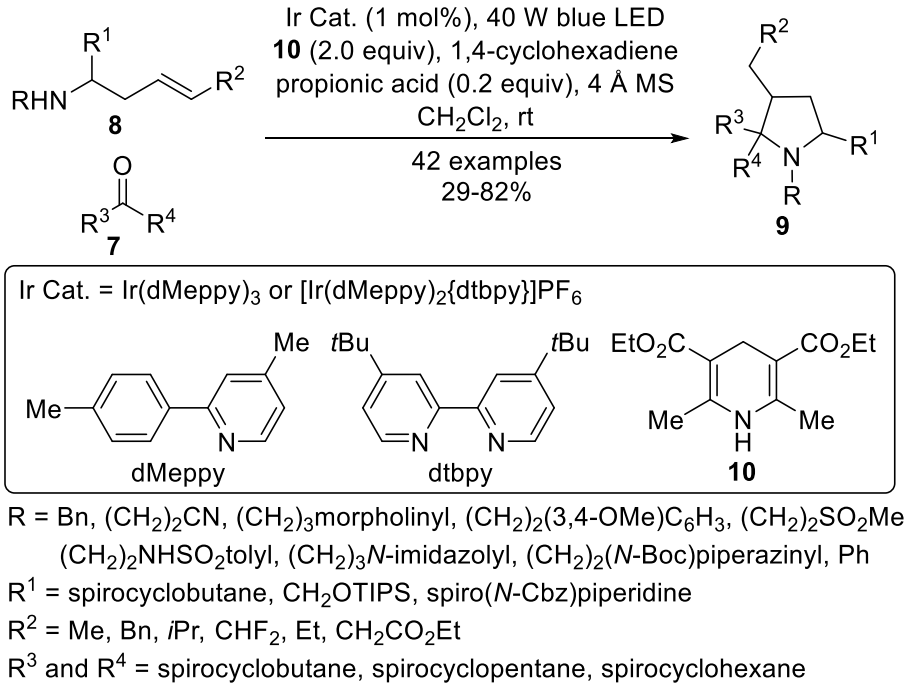
Scheme 1.1 Synthesis of functionalised cyclobutanes from sulphoxide **1**.[5]

Further work by the group showed that this synthetic methodology can also be applied to generate functionalised azetidine frameworks, by substituting sulphoxide **1** for analogous azabicyclo[1.1.0]butyl sulphoxide **4**.[6] Instead of a palladium catalysed strain release, they were able to use acetic acid to open the [1.1.0] ring system and generate the acetic acid salt. After a simple 'silica catch' purification the compounds could then be treated with Boc anhydride to give the corresponding protected azetidines (Scheme 1.2). They further showed that a variety of nitrogen functionalisation reactions could be applied to these systems as well as transformations of the boronic acid.



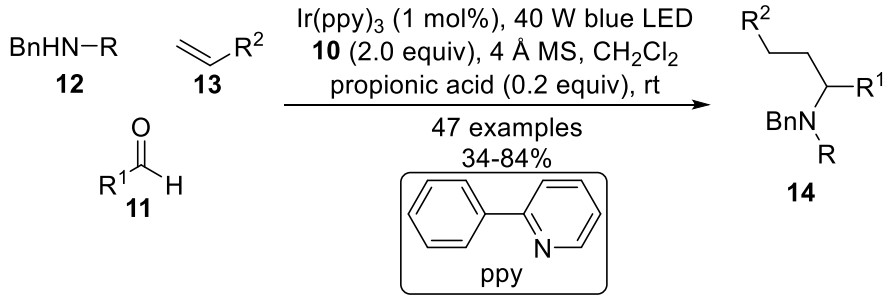
Scheme 1.2 Synthesis of functionalised azetidine frameworks from **4**.[6]

Work by Gaunt *et al.* has focused on the pyrrolidine framework, and by using spirocycles they were able to generate conformationally restricted scaffolds that are sp^3-rich. They used iridium photocatalysts $Ir(dmeppy)_3$ or $[Ir(dmeppy)_2\{dtbpy\}]PF_6$ with Hantzch ester **10** to react homoallyl amines **8** with ketones **7**.[7] By varying these two components they were able to generate forty-two different pyrrolidine scaffolds (**9**), showing the exceptional functional group tolerance of this process (Scheme 1.3).



Scheme 1.3 Synthesis of spirocyclic pyrrolidines **9** with Ir photocatalysis.[7]

They subsequently used this iridium photochemistry to generate functionally diverse tertiary alkylamines **14**, which are also sp^3-rich, although not as conformationally constrained as the pyrrolidine examples. They again used a low catalyst loading of a structurally similar $Ir(ppy)_3$ iridium catalyst with Hantzch ester **10**.[8] This time they combined benzylamines **12** with aldehydes **11** and alkenes **13** to generate the tertiary centre, again showing that this process tolerates a wide range of functional groups on all three reactants (Scheme 1.4).



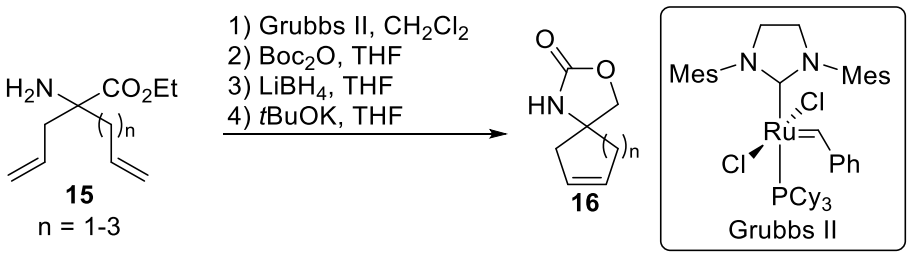
R = Bn, $CH_2(3\text{-}CO_2Et)C_6H_4$, CH_2Ar, *n*Bu, *i*Pr, $(CH_2)_2CN$, $(CH_2)_2OTIPS$ oxetane, CH_2CO_2Et

R^1 = *n*Pr, $(CH_2)_2CO_2Me$, $(CH_2)_2Ph$, *i*Pr, cyclohexyl, (*N*-Boc)piperazinyl tetrahydro-2*H*-pyranyl, (*N*-Boc)azetidinyl, H

R^2 = CO_2tBu, CO_2Bn, SO_2Ph, CN, $PO(OEt)_2$, 2-pyridyl, 4-pyridyl

Scheme 1.4 Synthesis of tertiary alkylamines **14** using Ir photocatalysis.[8]

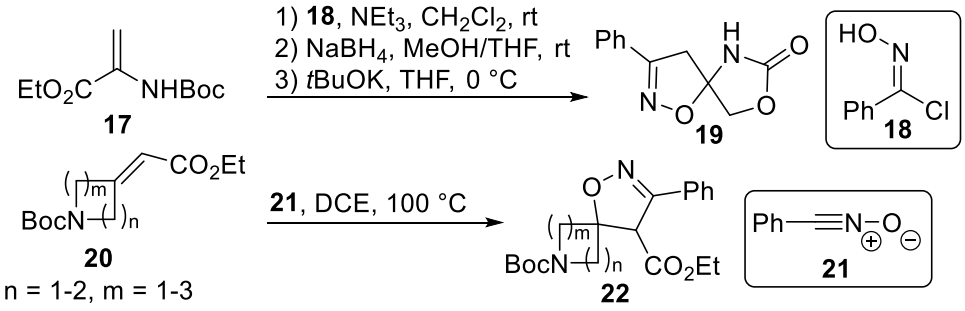
Spring *et al.* reported the synthesis of spirocyclic heterocycles and carbocycles as sp^3-rich frameworks, and demonstrated they are highly rigid, three-dimensional scaffolds that can be further diversified.[9] Building blocks **15** were chosen as the starting point, as Grubbs ring closing metathesis could be used to form the carbocycles, while Boc protection, ester reduction and cyclisation was used to generate an oxazolidine moiety for the second ring and give **16** (Scheme 1.5). They also showed that other similar heterocycles could be generated by modifying the cyclisation precursor. The double bond of the carbocycle was then functionalised using various well-precedented reactions, including Wacker oxidation, dihydroxylation, epoxidation, aziridination and bromination. Analysis using LLAMA (see section 4.2) showed that these fragments possess excellent shape diversity and three-dimensionality.



Scheme 1.5 Synthesis of spirocyclic scaffolds **16**.[9]

They also used cycloaddition chemistry to generate complementary spirocyclic scaffolds from acyclic, electron rich alkene **17** and hydroxylamine

18, which gave a dihydroisoxazole intermediate which was not isolated.[10] This substrate could then be converted to spirocycle **19** by carbamate formation (Scheme 1.6). They also used electron poor cyclic amines **20** for the cycloaddition reaction with nitrile oxide **21**, which gave spirocyclic amine scaffolds **22**.



Scheme 1.6 Synthesis of spirocycles using cycloaddition reactions.[10]

1.3 Cyclic Hydrazines in Medicinal Chemistry

Cyclic hydrazines are a class of heterocycle, containing two adjacent nitrogens along with one or more carbon atoms. The five most widely studied cyclic hydrazines are: diaziridines, diazetidines, pyrazolidines, hexahydropyridazines and diazepines (Figure 1.3).

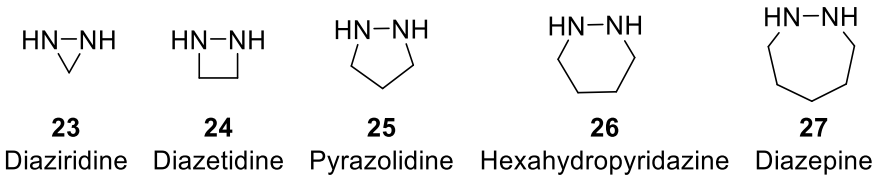


Figure 1.3 The five most commonly studied cyclic hydrazines.

There have been many synthetic routes developed to access this class of compound (*vide infra*), including a number of enantioselective methods. Their structure offers a lot of potential for the development of novel drug scaffolds. Cyclic hydrazines could potentially be used to provide non-planar, sp^3-rich scaffolds, with opportunities to diversify the ring at multiple locations and develop libraries of chemically novel scaffolds. As explored in this thesis, the use of substituents on the carbon adjacent to the hydrazine moiety (C3) is likely

to provide molecules which display their chirality in an orchestrated way (see section 1.9).

Other heterocycles including thiazolidines,[11,12] diazabicyclooctanes,[13] azetidines,[14] oxetanes[15] and other sp^3-rich frameworks (*vide supra*) are currently the subject of much interest in medicinal chemistry, due to their structural novelty and enhanced physiochemical and pharmacokinetic properties they often confer on drug leads.

Hydrazines have only been used a handful of times in approved pharmaceuticals, which may be due to the perception that they are toxic and challenging to manufacture safely (hydrazine itself is an extremely combustible and hazardous chemical and is often used as rocket fuel).[17] There are several bioactive natural products (including sanglifehrin A **28**[19] and actinoramide A **30**[18]) that contain the cyclic hydrazine moiety (Figure 1.4), in addition to proprietary lead compound **29**[20] and a small number of approved drugs (e.g. cilazapril **31**[21]). Access to a novel library of cyclic hydrazines would also open up new areas of intellectual property space, which is a key issue confronting the pharmaceutical industry, with patent busting approaches becoming prevalent.[16]

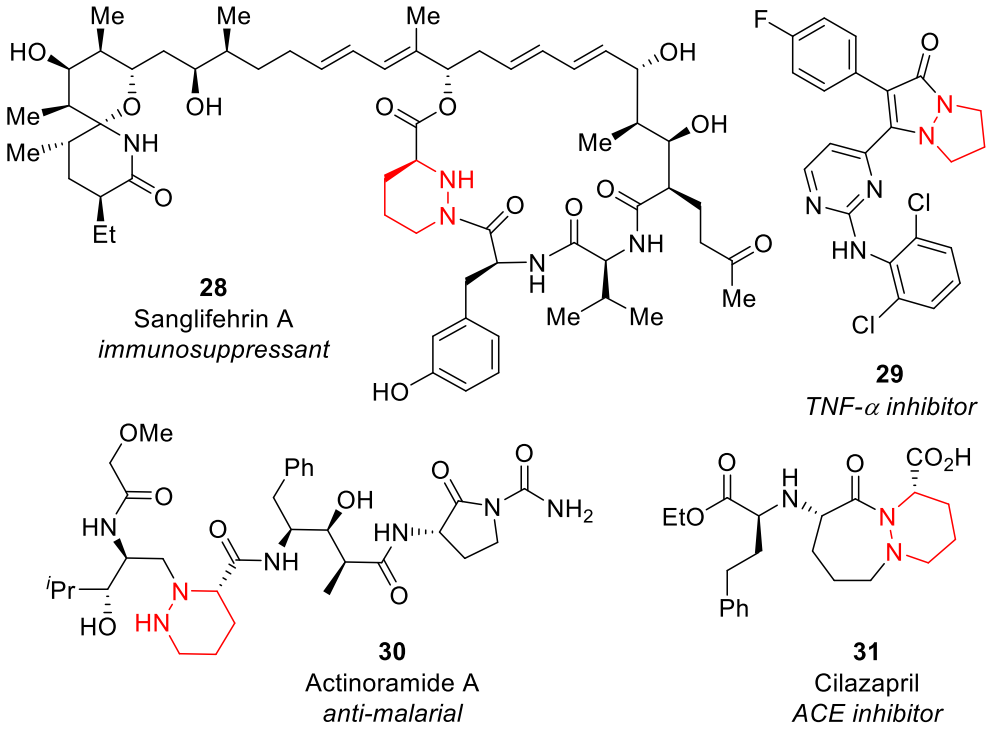
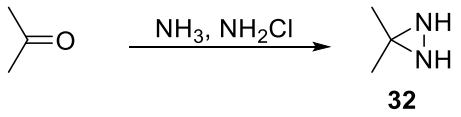


Figure 1.4 Hydrazine containing natural products, proprietary lead compounds and drugs.

There are a number of reviews on the synthesis of hydrazines[22, 23] and cyclic hydrazines.[24] Here we introduce the more common methods for the synthesis of each ring size, with a focus on enantioselective syntheses of substituted cyclic hydrazines.

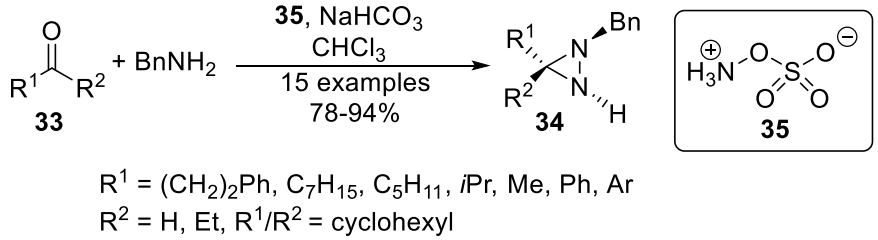
1.4 Synthesis of Diaziridines

The application of diaziridines is not described in this thesis, however their synthesis has been described in the literature. Here we present a small selection of these synthetic approaches, focusing on more recent publications. The first synthesis of a diaziridine was reported in 1961 when Schmidt used acetone, ammonia and chloramine to synthesise 3,3-dimethyl-1,2-diaziridine **32** (Scheme 1.7).[25]



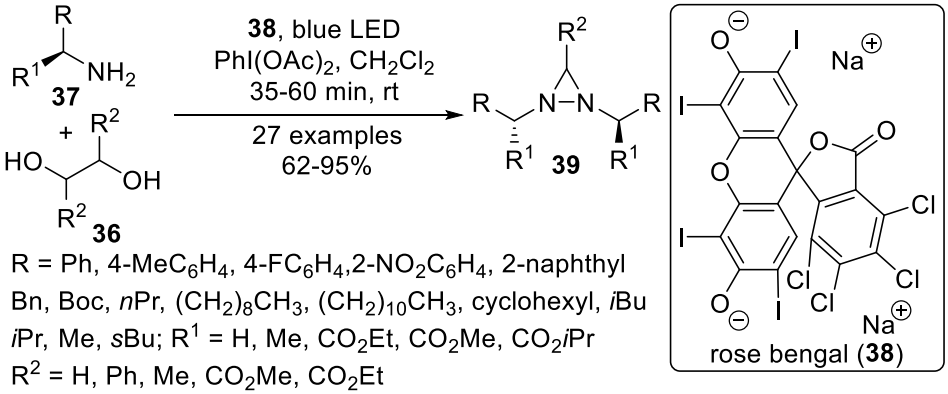
Scheme 1.7 Synthesis of 3,3-dimethyl-1,2-diaziridine **32**.[25]

Combining a carbonyl compound with an amine nucleophile is still a commonly used method to access diaziridines. Moura-Letts *et al.* used hydroxylamine-*O*-sulfonic acid (**35**) as their aminating reagent and screened a variety of solvents and additives, using benzyl amine and various aldehydes and ketones as substrates.[26] They showed that adding an inorganic base was much more effective than an organic one, with $NaHCO_3$ proving to be the most effective base. Using their optimised conditions, they were able to generate a series of diaziridines **34** diastereoselectively (Scheme 1.8).



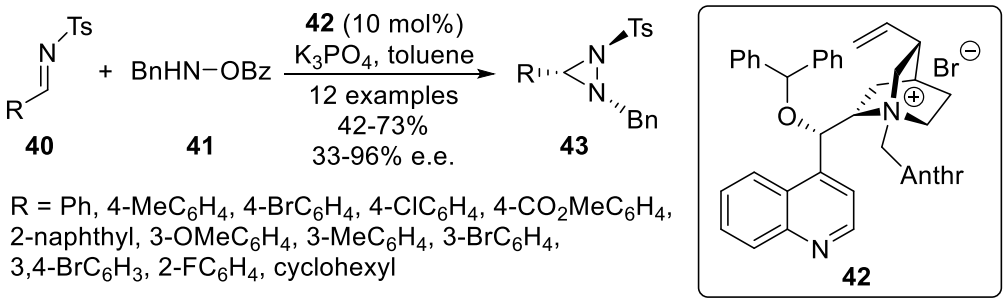
Scheme 1.8 Synthesis of diaziridines **34** using HOSA.[26]

Maiti *et al.* developed a photocatalytic method, to generate diaziridines **39**.[27] They used rose bengal (**38**) as photocatalyst, which was excited using blue LEDs (Scheme 1.9). This was used in combination with the oxidising agent (diacetoxyiodo)benzene, to catalyse the reaction of alkyl amines **37** with 1,2-diols **36**. They synthesised a diverse library containing 27 diaziridines, including examples with chiral substituents on the nitrogens.



Scheme 1.9 Synthesis of diaziridines **39** using rose bengal (**38**) as a photocatalyst.[27]

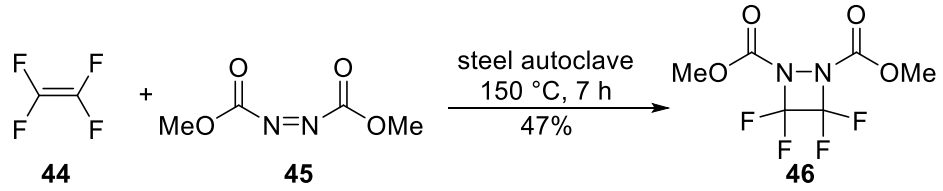
Other recent approaches have shown it is possible to synthesise diaziridines enantioselectively. Jørgensen *et al.* have developed a method for enantioselective diaziridination of *N*-tosyl aldimines **40**, which utilises chiral phase transfer catalyst **42** in order to generate diaziridines **43** in moderate to good yields, and excellent enantioselectivity (Scheme 1.10).[28] Generally, the enantioselectivity was highest for *meta*- and *para*-substituted aromatic rings, while *ortho*-substituted compounds and cyclohexyl displayed inferior enantiomeric enrichment. The group were also able to demonstrate that orthogonal deprotection of both nitrogen atoms was feasible. Computational data suggested that ring inversion of the diaziridine products was a high energy process (>85 kJ mol^{-1} according to DFT calculations) and thus unlikely to occur.



Scheme 1.10 Synthesis of diaziridines **43** *via* enantioselective diaziridination.[28]

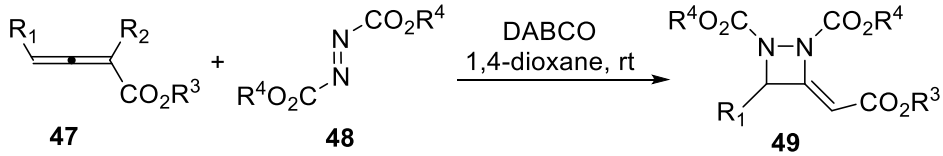
1.5 Synthesis of Diazetidines

Diazetidines represent a challenging synthetic target, as they are a highly strained heterocycle, however a number of approaches have been reported, generally by using either a [2+2] cycloaddition or a ring closure strategy. The first synthesis of a diazetidine was reported in 1960 by Kauer and Schneider.[29] The concerted [2+2] cycloaddition of **44** and **45** is forbidden by the Woodward-Hoffman rules[30, 31] but still gave diazetidine **46**, suggesting this is a step-wise and not a concerted process (Scheme 1.11).



Scheme 1.11 Synthesis of **46** using a [2+2] cycloaddition reaction.[29]

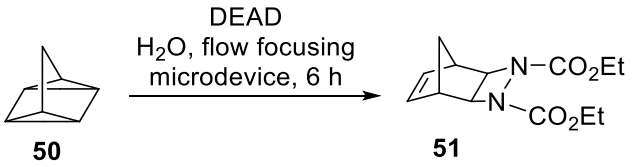
More recently Tang *et al.* have developed another [2+2] route to diazetidines **49**, *via* the reaction of an allenoates **47** with azodicarboxylates **48**.[32] This method was effective for a wide variety of allenoates and azodicarboxylates and also generated the *Z* isomers with high selectivity (Scheme 1.12).



R^1 = H, Me, Et, Bn, C_6H_{13}; R^2 = H, Me, CH_2CO_2Et; R^3 = Bn, Et;
R^4 = *i*Pr, Et, *t*Bu

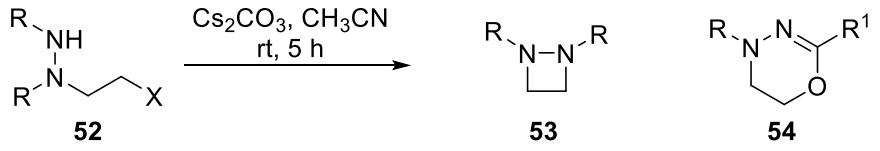
Scheme 1.12 Synthesis of diazetidines **49** *via* a DABCO catalysed process.[32]

Zheng *et al.* synthesised tricyclic diazetidine **51** by [2+2] cycloaddition as part of a study into reaction acceleration using the 'on water reaction'[33] (Scheme 1.13).[34] To study the effects, they explored the reaction of DEAD with **50**. The reaction was carried out in a flow focusing microdevice, but detailed characterisation of the product was not attempted as the purpose of the study was to study the reaction kinetics.



Scheme 1.13 Reaction of **50** with DEAD to give tricyclic diazetidine **51**.[34]

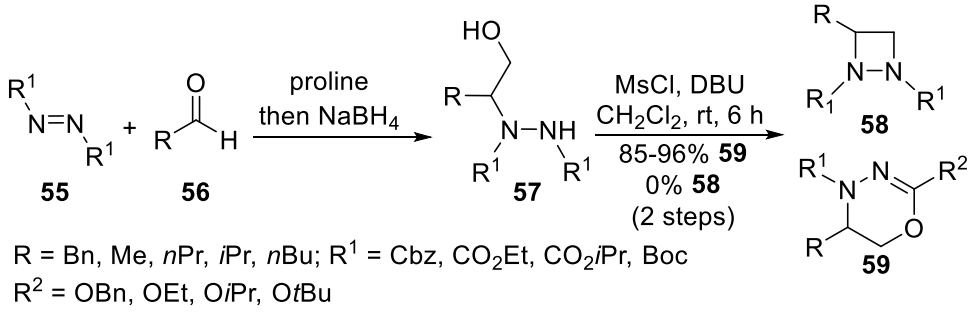
The synthesis of diazetidines by ring closure has also been reported. Previous work in the Shipman group investigated the ring-closure reaction using a variety of substrates.[35] It was found that there is competition between closure through the carbamate oxygen to give oxadiazine (**54**), and closure to give the desired diazetidine (**53**). Using softer leaving groups tended to give a higher yield of the diazetidine, and larger and more diffuse cations tended to favour formation of the diazetidine. The best results were obtained using an iodide leaving group and caesium carbonate as the base, however, even under optimised conditions the desired diazetidine **53** was obtained in a relatively modest 50% yield, with oxadiazine **54** as the undesired by-product (Scheme 1.14). Using sulphonamides instead of carbamates improved the reaction further, with 98% yield obtained when R = Ts, as it is not possible to form an oxadiazine in this case.



R = Cbz, X = I, R^1 = OBn: **53** = 50%, **54** = 42%
R = Boc, X = I, R^1 = O*t*Bu: **53** = 48%, **54** = 45%
R = Ms, X = OMs: **53** = 13%
R = Ts, X = I: **53** = 98%

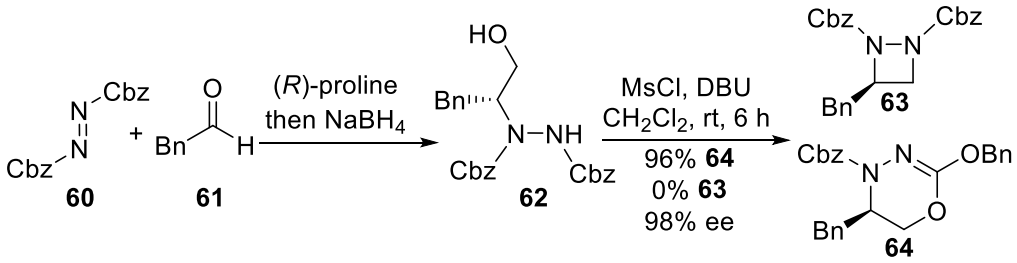
Scheme 1.14 Optimised synthesis of 1,2-diazetidines **53**.[35]

This corrected earlier work carried out by Ma *et al.*,[36] who attempted to synthesise a series of 1,2-diazetidines **58** using diazodicarboxylates **55** and aldehydes **56** to generate alcohol precursors **57**. These substrates were then cyclised *via* an intramolecular Mitsonobu reaction, with the overall yields for this 2-step process above 85% (Scheme 1.15). However, it was shown by Shipman that they had misassigned the product structures and actually synthesised the corresponding oxadiazines **59**.



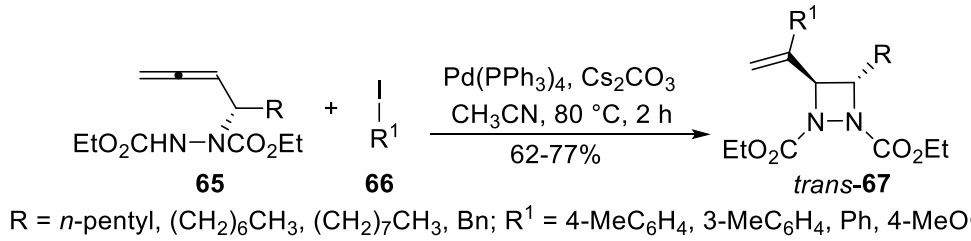
Scheme 1.15 Attempted synthesis of diazetidines **58**.[36]

In addition, they also reported an enantioselective synthesis of diazetidine **63** by using (*R*)-proline in the amination reaction; the product was formed in 96% yield (Scheme 1.16). Again however, this was actually forming the corresponding oxadiazine **64** and was not diazetidine **63**.



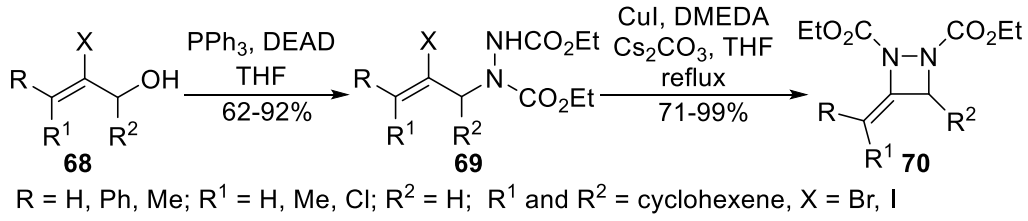
Scheme 1.16 Attempted synthesis of diazetidine **63** which gave oxadiazine **64**.[36]

Subsequently Ma *et al.* published examples of diazetidine synthesis, *via* the cyclisation reaction of 2,3-allenylic hydrazines **65** with aryl iodides **66**, catalysed by $Pd(PPh_3)_4$.[37] After screening a variety of bases, it was found that Cs_2CO_3 was the most effective base for the Heck reaction. These conditions were used to synthesise a variety of diazetidines **67** in good yields and with complete selectivity for the *trans* product (Scheme 1.17).



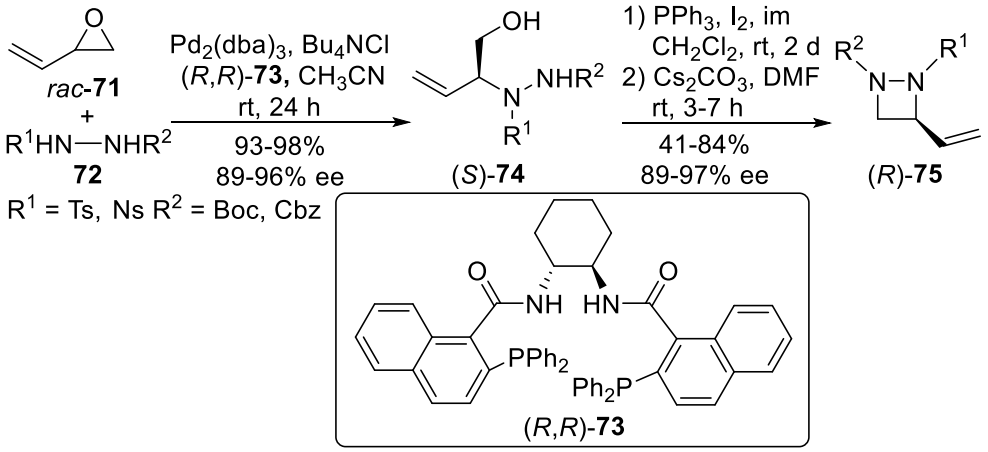
Scheme 1.17 Synthesis of diazetidines **67** using a Heck reaction.[37]

There has also been more recent work in the Shipman group, including the synthesis of a series of 3-methylene-1,2-diazetidines **70** using a copper catalysed ring closure of 2-halo-2-propenyl hydrazines **69**.[38] The hydrazine containing cyclisation precursors were prepared by Mitsonobu reaction of allyl alcohol precursors **68**. Using this approach, a series of precursors were generated. The cyclisation process was most successful using allyl bromides, and in the presence of caesium carbonate, DMEDA and CuI, diazetidines **70** were produced in excellent yields (Scheme 1.18). This efficient 2-step process provided a useful route to diazetidines which contain an exocyclic double bond, allowing for further functionalisation.



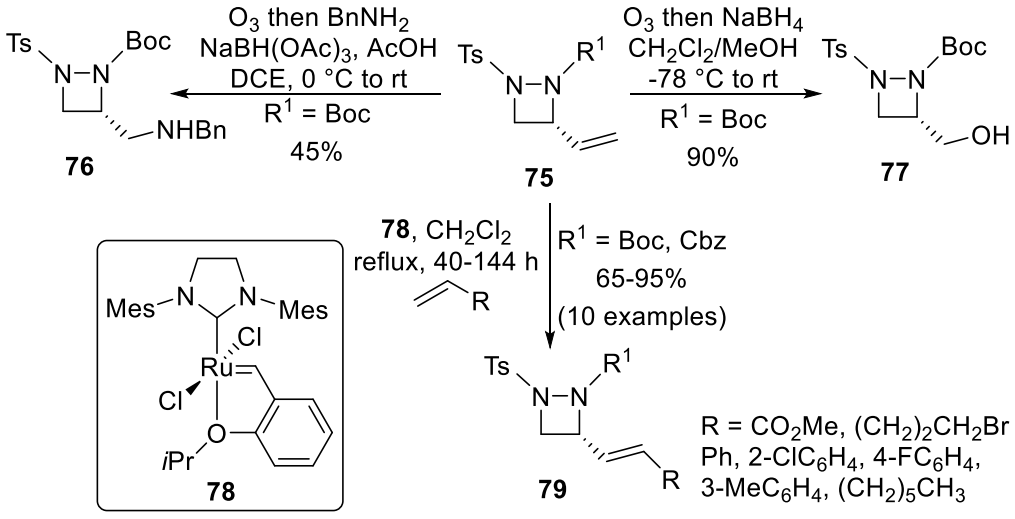
Scheme 1.18 Copper catalysed ring-closure to form 1,2-diazetidines **70**.[38]

Subsequently, the Shipman group have developed an enantioselective route to substituted diazetidines, which uses *rac*-vinyl epoxides **71** as the starting material.[39] Opening **71** with protected hydrazines **72** using palladium chemistry developed by Trost *et al*.[40] gave intermediate **74**, followed by cyclisation using a Mitsunobu reaction to vinyl 1,2-diazetidines **75** (Scheme 1.19).



Scheme 1.19 Enantioselective synthesis of vinyl 1,2-diazetidines **75**.[39]

It was subsequently shown that vinyl diazetidines **75** could be functionalised in a variety of ways, in order to diversify the substituent at C3. Cross-metathesis using Grubbs-Hoyveda catalyst **78** was used to react vinyl 1,2-diazetidines **75** with terminal alkene coupling partners to give **79**. In addition, ozonolysis was used to cleave the vinyl group of **75** to an aldehyde, which could then be transformed into amine **76** using reductive amination, or to alcohol **77** *via* a sodium borohydride reduction (Scheme 1.20).

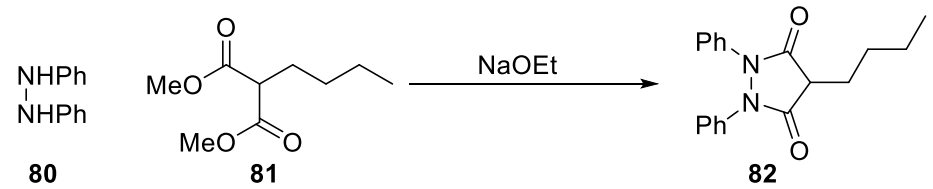


Scheme 1.20 Functionalisation of vinyl diazetidines.[39]

1.6 Synthesis of Pyrazolidines

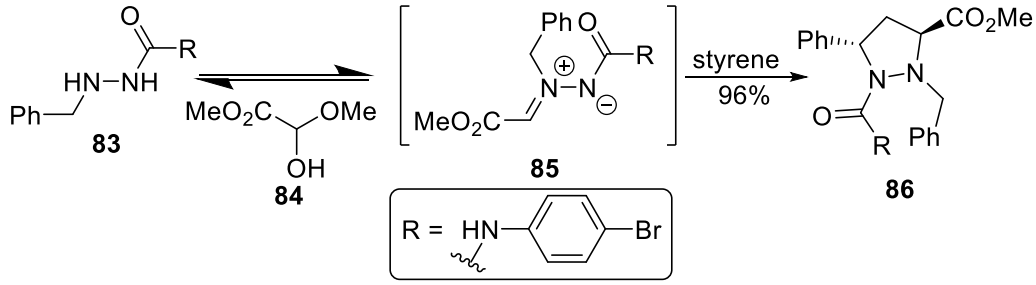
The synthesis of pyrazolidines has been more widely reported than for corresponding smaller ring sizes, as the synthesis of less strained 5-membered

rings is generally less challenging. They are typically synthesised either by [3+2] cycloaddition or by ring closure in a similar manner to diazetidines. The first reported synthesis of pyrazolidine **25** itself was in 1943 by Buhle *et al.*[41] who combined 1,3-dibromopropane with hydrazine. The first example of a pyrazolidine based drug, phenylbutazone (**82**), was synthesised shortly after World War Two and approved for human use as a highly effective NSAID (Non-Steroidal Anti-Inflammatory Drug).[42] It was synthesised by the condensation of **80** and **81** in the presence of sodium ethoxide (Scheme 1.21).



Scheme 1.21 Synthesis of phenylbutazone (**82**).[42]

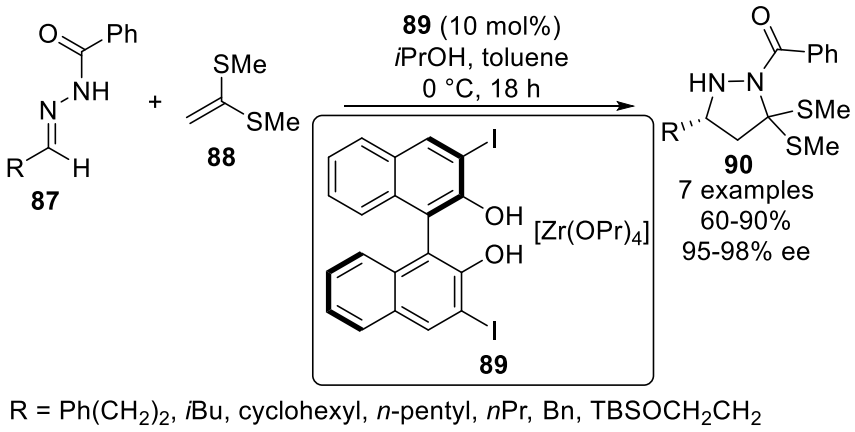
Since these early efforts, several other methodologies have been developed to synthesise more structurally complex examples of pyrazolidines. The synthesis of pyrazolidines by [3+2] cycloaddition has been utilised as it is a simple and highly effective method that generates complex pyrazolidines in a single step. Work by Kau and Martinelli showed it was possible to generate highly functionalised pyrazolidines using semicarbazide **83**.[43] Reacting this with methyl glyoxylate hemiacetal (**84**) formed intermediate **85**, which could then be trapped with styrene to give pyrazolidine **86** in an excellent yield (Scheme 1.22).



Scheme 1.22 Synthesis of pyrazolidine **86** via a [3+2] cycloaddition.[43]

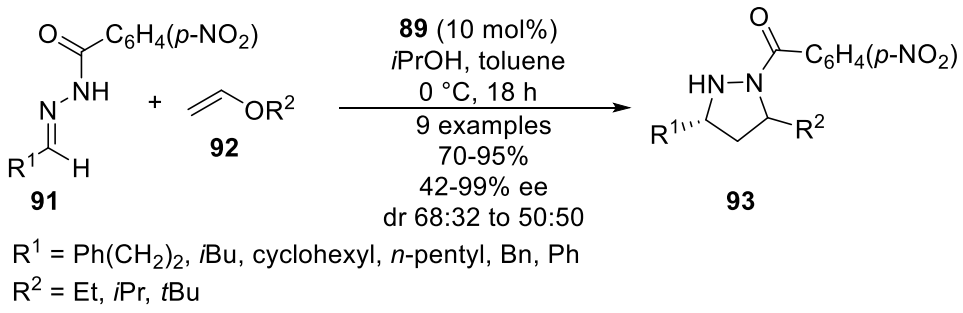
In 2004 Kobayashi and Yamashita developed a highly enantioselective method for the synthesis of highly substituted pyrazolidines, utilising chiral zirconium catalyst **89**.[44] This was shown to be an effective catalyst for the

reaction of hydrazones **87** with ketene dimethyl dithioacetal **88**, which gave the desired pyrazolidines **90** in good to excellent yields and with excellent enantioselectivity (Scheme 1.23). They were able to provide evidence for a [3+2] mechanism (as opposed to a stepwise one), by changing R for much bulkier groups. This gave a significant reduction in reaction rate which was consistent with a concerted mechanism.



Scheme 1.23 Enantioselective synthesis of pyrazolidines **90** using Zr catalyst **89**.[44]

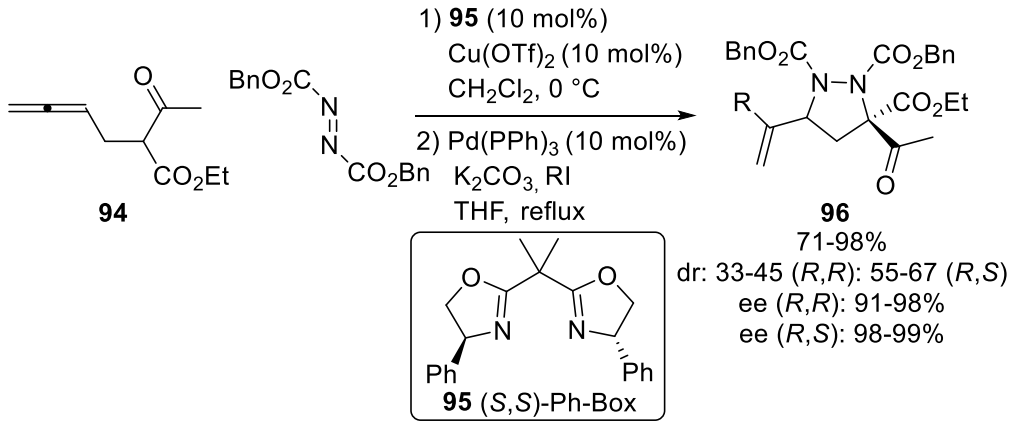
This methodology was also shown to be effective in the reaction of vinyl ethers **92** with hydrazones **91**. This transformation introduced a second stereocentre into the final pyrazolidines **93**, and although these were only obtained with moderate diastereoselectivities, the ees and yields were generally excellent (Scheme 1.24).



Scheme 1.24 Synthesis of pyrazolidines **93** using Zr catalyst **89**.[44]

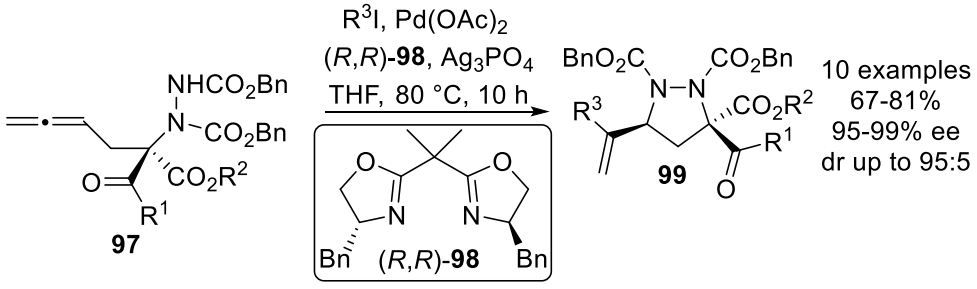
Ma *et al.* used a palladium and copper catalysed reaction to construct highly substituted pyrazolidines.[45] Using $Pd(PPh_3)_4$, CuOTf and chiral ligand (*S*,*S*)-Ph-Box **95** they were able to effect an enantioselective amination of allene **94** with

DBAD. The mechanism proceeds *via* carbopalladation to generate a π-allyl palladium intermediate, which is trapped by an intramolecular coupling to generate functionalised pyrazolidines **96**. This was completed with excellent yields and enantioselectivities, but only modest diastereoselectivity (Scheme 1.25).



Scheme 1.25 Synthesis of substituted pyrazoldines **96** using a Pd and Cu catalysed process.[45]

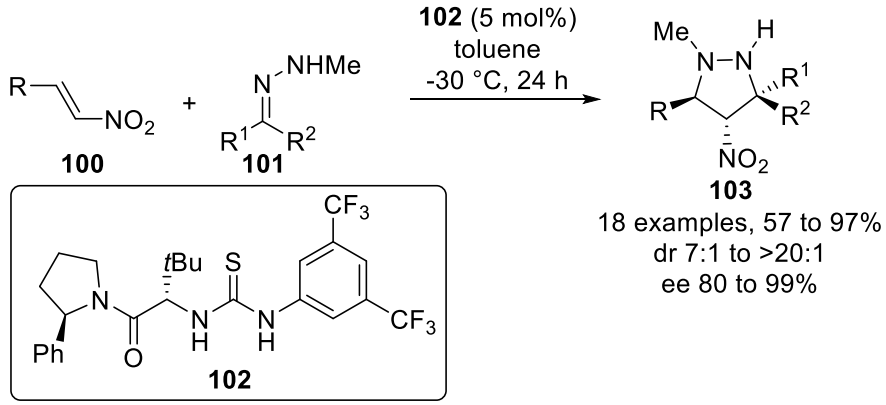
Ma *et al.* followed this work with a similar strategy to synthesise pyrazolidines.[46] Using palladium acetate and ligand (*R,R*)-**98**, they were able to synthesise ten examples of highly functionalised pyrazolidines **99** in good yields (Scheme 1.26). The enantioselectivity of the process was excellent across all the examples and was more diastereoselective than their previous work.



Scheme 1.26 Synthesis of pyrazolidines **99** using Pd-catalysed cyclisation.[46]

Jørgensen and co-workers developed an organocatalysed [3+2] cycloaddition of a nitro-olefin **100** with a hydrazone **101**.[47] By utilising organocatalyst **102**

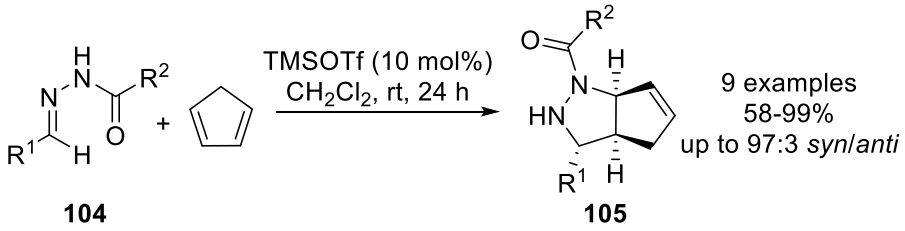
they were able to synthesise a series of 4-nitropyrazolidines **103** which were formed using a hydrogen bond catalysed 1,3-dipolar cycloaddition. They were able to synthesise eighteen different products bearing a variety of functional groups with excellent yields and selectivity (Scheme 1.27).



R = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 3-$OMeC_6H_4$, 2-ClC_6H_4, 2-naphthyl, 3,4-$Cl_2C_6H_3$
3-pyridyl, 2-thiophenyl, cyclohexyl, *n*Bu; R^1 = 4-ClC_6H_4, Ph, 3-$OMeC_6H_4$
4-BrC_6H_4, 2,3,4-$Cl_3C_6H_2$, *i*Pr; R^2 = Me, Et; R^1 = R^2 = cyclohexyl

Scheme 1.27 Synthesis of 4-nitropyrazolidines **103** using organocatalyst **102**.[47]

Tsogoeva *et al.* developed an efficient method to construct fused bicyclic pyrazolidines by utilising the Lewis acid TMSOTf to catalyse the [3+2] cycloaddition of hydrazones **104** with cyclopentadiene.[48] Using 10 mol% of the Lewis acid, they were able to synthesise nine pyrazolidines **105** in generally excellent yields, with the reaction found to form the *syn* product (Scheme 1.28).

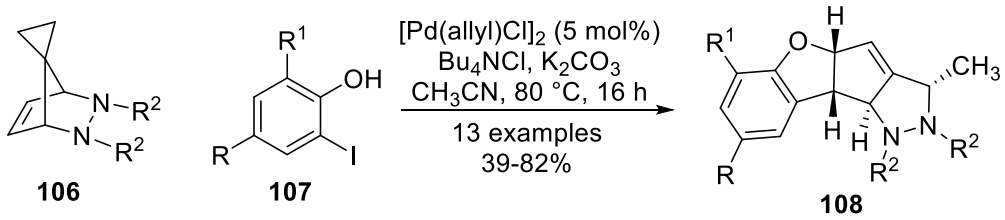


R^1 = CO_2Et, $Ph(CH_2)_2$, *i*Bu, Et, Bn; R^2 = 4-$NO_2C_6H_4$, Ph, 4-BrC_6H_4

Scheme 1.28 Synthesis of fused bicyclic pyrazolidines **105**.[48]

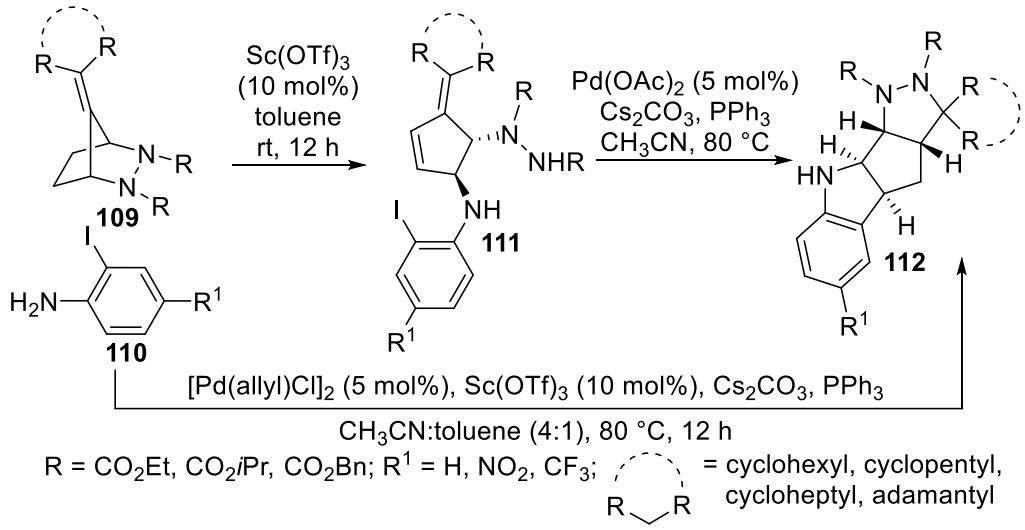
Radhakrishnan *et al.* developed a catalytic domino process to synthesise tetracyclic pyrazolidine systems.[49] The synthesis utilises a palladium catalysed reaction between *ortho*-iodophenols **107** with spirocyclic olefins **106** bearing a cyclopropane ring (Scheme 1.29). This system is set up to undergo a complex

domino process where the palladium first catalyses a Heck reaction to form a bicylic intermediate. The phenol oxygen triggers the ring opening of the bicycle, before further palladium catalysed processes provides **108**.



Scheme 1.29 Synthesis of tetracyclic pyrazolidines **108** using a catalytic domino process.[49]

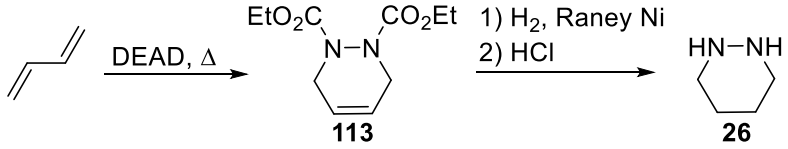
In a subsequent paper, the same group described a similar process, demonstrating the synthesis of spirocyclic pyrazolidines **112**.[50] This time they mainly focused on a 2-step process, first utilising a Lewis acid catalysed desymmetrisation of a fulvene derived diazabicyclic olefin **109**. This process could be used to synthesise a variety of cyclisation precursors **111** (Scheme 1.30). This precursor could then undergo a tandem cyclisation process catalysed by palladium to yield **112**. Finally, they also synthesised several examples using a one-pot process.



Scheme 1.30 Synthesis of spirocyclic pyrazolidines **112** using Lewis acid and Pd catalysis.[50]

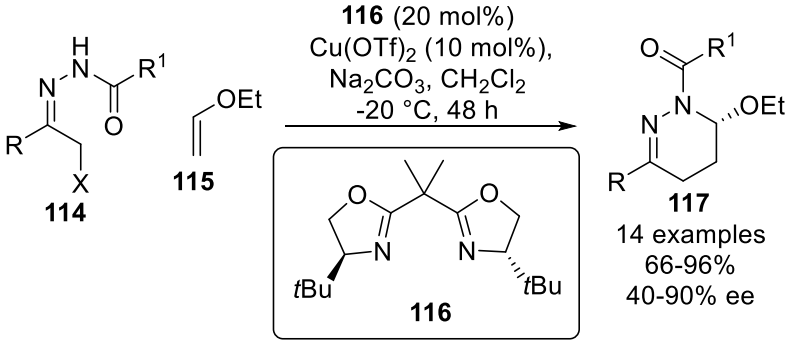
1.7 Synthesis of Hexahydropyridazines

The first synthesis of hexahydropyridazine **26** was reported by Alder and Niklas in 1954.[51] They heated buta-1,3-diene with DEAD to give tetrahydropyridazine **113**, which could then be converted to **26** by reducing the double bond with Raney Nickel followed by hydrolysis with HCl (Scheme 1.31). This kind of concerted cycloaddition is rarely used in more modern synthetic strategies, which tend to be sequential processes with a final ring closure step.



Scheme 1.31 The first synthesis of hexahydropyridazine **26**.[51]

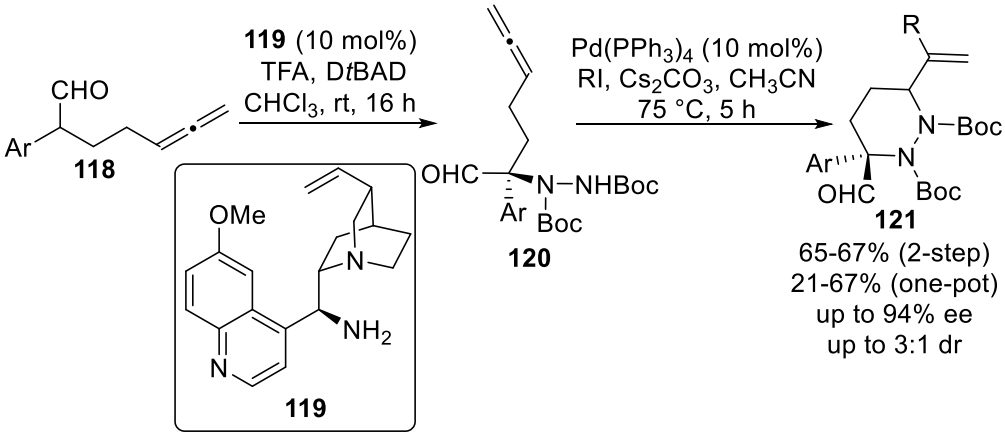
There are however some more modern cycloaddition approaches that give tetrahydropyridazines. Work by Xiao *et al.* demonstrated that tetrahydropyridazines could be synthesised enantioselectively using an Inverse Electron-Demand hetero-Diels-Alder (IEDDA) reaction (Scheme 1.32).[52] Combining hydrazones **114** with ethyl vinyl ether **115** gave tetrahydropyridazines **117** in excellent yield and with good enantioselectivity when ligand **116** was employed.



Scheme 1.32 Synthesis of tetrahydropyridazines **117** using the IEDDA reaction.[52]

Recent work by Moreau *et al.* has shown that a multicatalytic approach can be used to assemble hexahydropyridazine scaffolds (Scheme 1.33).[53] Starting

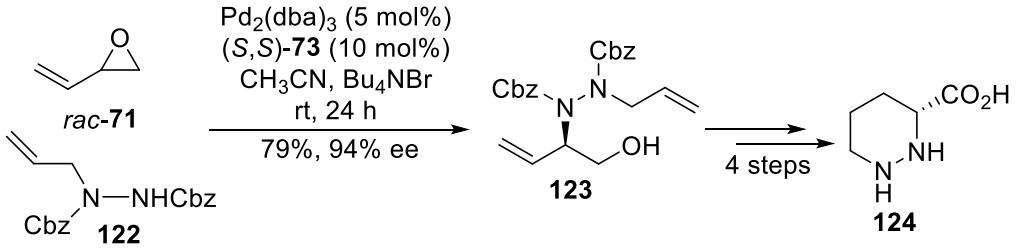
with a stereoselective α-amination of aldehydes **118** catalysed by organocatalyst **119** they synthesised hydrazine intermediates **120**. This intermediate could then be converted to a hexahydropyridazine using a palladium catalysed cyclisation to give hexahydropyridazines **121**. They were subsequently able to show that no purification of intermediate **120** was needed and that hexahydropyridazines **121** could be synthesised in similar overall yields using sequential multicatalysis. The enantioselectivity of the process was excellent (up to 94% ee), however the diastereoselectivity was more modest. They were also able to demonstrate that some variation in the aryl group of **118** and in the aryl iodide in the last step was tolerated.



Ar = Ph, 4-ClC_6H_4; R = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 4-$OMeC_6H_4$, 4-$CO_2EtC_6H_4$, 4-FC_6H_4, 4-$NO_2C_6H_4$

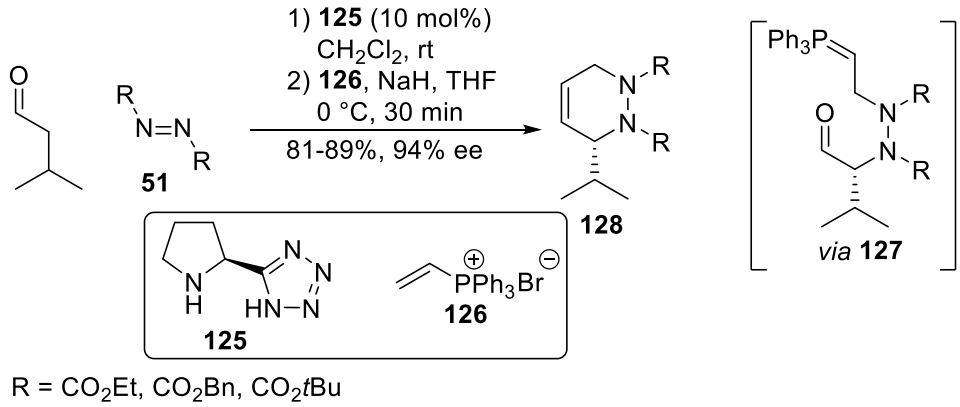
Scheme 1.33 Synthesis of hexahydropyridazines **121** with organocatalysis and Pd catalysis.[53]

Mangion *et al.* reported the synthesis of unnatural amino acid (*R*)-piperazic acid (**124**),[54] with the ring opening of vinyl epoxide (**71**) using catalyst **73**[40] (Scheme 1.34). The opening of vinyl epoxide with an allyl substituted protected hydrazine **122** was optimised carefully and product **123** was isolated in good yield and with excellent enantioselectivity for the *R* enantiomer. After this, four further steps were required to synthesise (*R*)-piperazic acid (**124**), all of which were achieved with excellent yields.



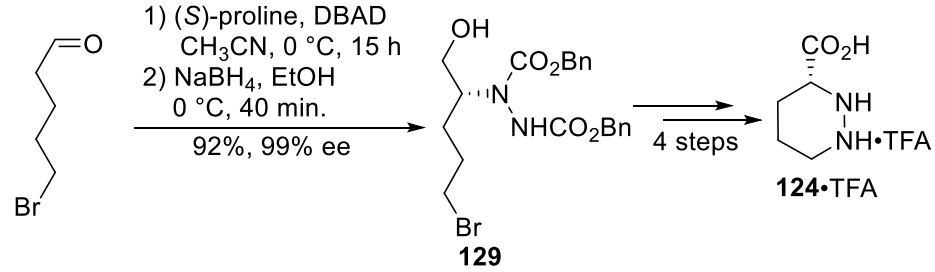
Scheme 1.34 Synthesis of (*R*)-piperazic acid (**124**) using Trost's ligand (*S*,*S*)-**73**.[54]

Ley *et al.* synthesised chiral tetrahydropyridazines in a one-pot process by utilising organocatalyst **125**.[55] Initially they used isovaleraldehyde which underwent α-hydrazination with azodicarboxylates **51** before reacting *in situ* with vinyl phosphonium salt **126** to give **127** which was not isolated. This intermediate underwent *in situ* an intramolecular Wittig reaction to give tetrahydropyridazines **128** (Scheme 1.35).



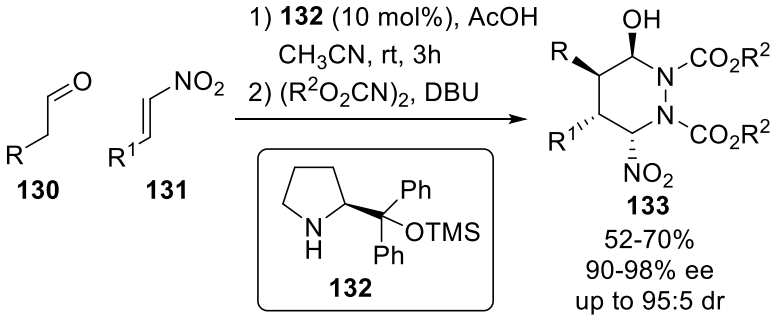
Scheme 1.35 One-pot synthesis of tetrahydropyridazines **128**.[55]

Similar work by Hamada *et al.* also exploited the organocatalysed α-hydrazination of 5-bromopentanal with DBAD.[56] Using (*S*)-proline as the organocatalyst they were able to generate a linear hydrazine precursor, which was immediately treated with sodium borohydride to reduce the aldehyde and give **129** in excellent yield and enantioselectivity (Scheme 1.36). Four additional steps were then required to transform **129** into the TFA salt of (*R*)-piperazic acid (**124**).



Scheme 1.36 Synthesis of the TFA salt of (R)-piperazic acid **124**.[56]

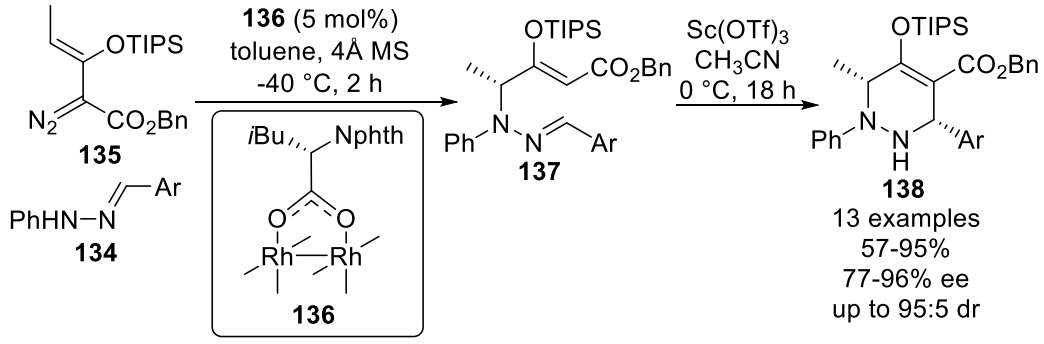
Jørgensen/Hayashi catalyst **132** was used by Han *et al.* to generate hexahydropyridazine based frameworks (Scheme 1.37).[57] Their strategy combined aldehydes **130**, with nitroolefins **131** and azodicarboxylates **51** which underwent an amine catalysed Michael reaction, then subsequent α-amination and intramolecular hemiaminalisation. After optimisation they were able to generate hexahydropyridazines (**133**) in good yield and with excellent enantioselectivity and diastereoselectivity across multiple examples.



R = Me, Et, *n*Pr, (*Z*)-CHC(CH$_3$)$_2$; R^1 = Ph, 2-ClC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 3,4-(OMe)C$_6$H$_3$, 2-furyl, 2-thiophenyl; R^2 = *i*Pr, Et, *t*Bu

Scheme 1.37 Synthesis of hexahydropyridazines **133**.[57]

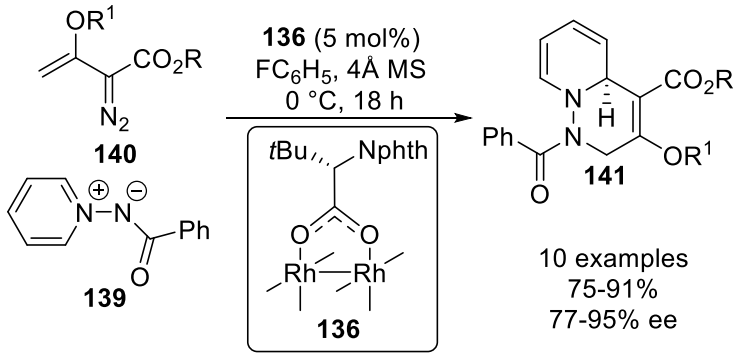
Doyle *et al.* used rhodium catalysed carbene chemistry with hydrazones to generate tetrahydropyridazines in a two-step process (Scheme 1.38).[58] Diazo compound **135** and hydrazones **134** reacted with rhodium catalyst **136**, but gave **137** instead of the desired tetrahydropyridazine **138**. After further optimisation of the cyclisation process, a Lewis acid catalysed Mannich reaction with scandium triflate yielded the desired tetrahydropyridazines **138** in excellent yield and without significant erosion of enantiopurity.



Ar = 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 4-$OMeC_6H_4$, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 2-furyl, 4-PhC_6H_4, 2-$(CF_3)C_6H_4$, 2,4,6-$Me_3C_6H_2$, 9-anthryl

Scheme 1.38 Synthesis of hexahydropyridazines **138** using rhodium catalyst **136**.[58]

Doyle *et al.* followed up on this work with a completely concerted process, this time utilising *N*-iminoquinolinium ylide **139** instead of hydrazones (Scheme 1.39).[59] Although this reaction involves a dearomatization process, it is driven by the reactivity of zwitterion **139**. After only minor changes to their optimised conditions they were able to isolate bicyclic products **141** in excellent yield and enantioselectivity.



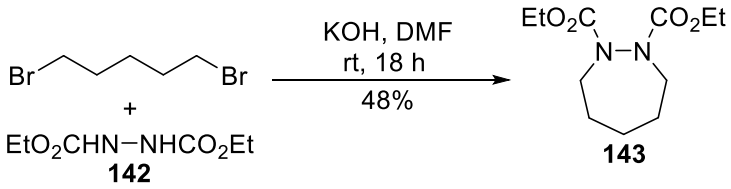
R = Me, *i*Pr, cyclohexyl, *t*Bu, Bn; R^1 = TBS, TIPS

Scheme 1.39 Synthesis of bicyclic tetrahydropyridazines **141** using rhodium catalyst **136**.[59]

1.8 Synthesis of Diazepines and Higher Homologues

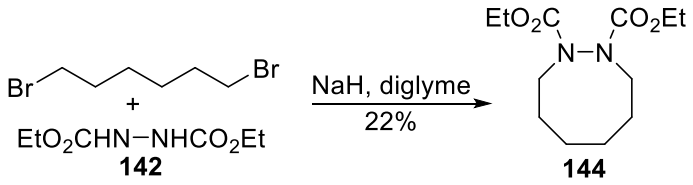
The synthesis of diazepines and larger ring homologues like diazocanes (8-membered cyclic hydrazines) have not been frequently reported in the literature. The first example of a diazepine appeared in 1962, when Zinner and Deucker reported the synthesis of diethyl 1,2-diazepine-1,2-dicarboxylate (**143**).[60] Their

synthesis combined **142** with 1,5-dibromopentane to yield the desired diazepine (Scheme 1.40).



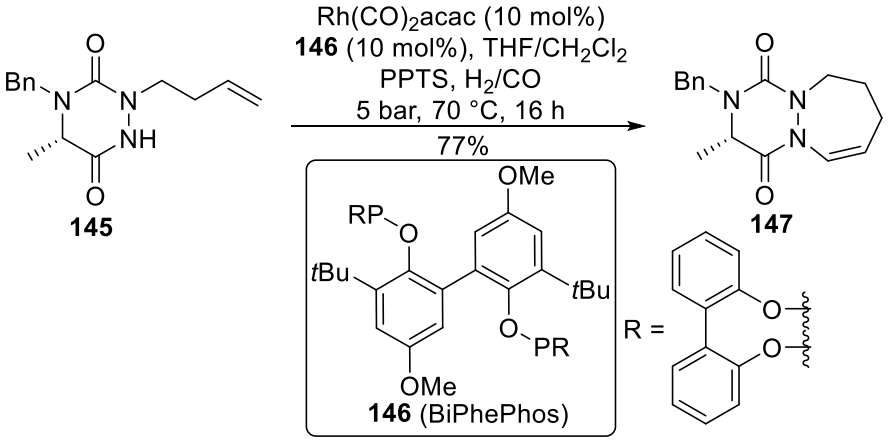
Scheme 1.40 First reported synthesis of a diazepine.[60]

A similar synthesis of diazocane **144** was first reported by Stoddard and Overberger in 1970.[61] They used 1,6-dibromohexane and hydrazine **142**, which were combined with sodium hydride in diglyme to give **144** in a modest 22% yield (Scheme 1.41). There have been a small number of other reported approaches to the synthesis of diazocanes[62] and larger rings,[63] however discussion of these systems is outside of the scope of this thesis and we will instead focus on diazepines.



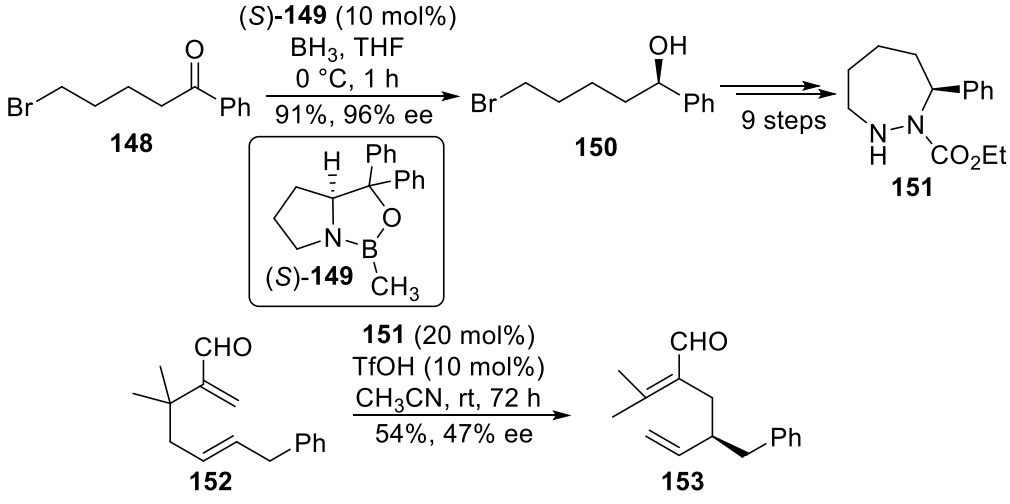
Scheme 1.41 First reported synthesis of a diazocane.[61]

Bonnet *et al.* reported a synthesis of bicyclic diazepine systems using a rhodium catalysed cyclohydrocarbonylation process (Scheme 1.42).[64] Using precursor **145**, which is derived from alanine, the cyclohydrocarbonylation gave bicyclic diazepine **147**, in good yield when BiPhePhos catalyst **146** was used. This process was also used on several similar systems, including tetrahydropyridazine examples.



Scheme 1.42 Synthesis of bicyclic diazepine **147** using a cyclohydrocarbonylation process.

Gleason and Caldre reported the synthesis of enantiomerically enriched diazepine **151** using a Corey-Bakshi-Shibata (CBS) reduction to reduce phenyl ketone precursor **148** to give alcohol **149** (Scheme 1.43).[65] The approach reported here has similarities to the approach we report in chapter 2 where we used ATH to generate alcohols enantioselectively (see Section 2.4). They used **151** as an organocatalyst for an asymmetric Cope rearrangement. Although the highest enantioselectivity of any of the organocatalysts tested was achieved with **151**, it was only able to afford rearranged product **153** in a modest yield of 54% and an enantiomeric excess of 47%.



Scheme 1.43 CBS reduction of ketone **148** as the key step in the synthesis of **151** and use of **151** as an organocatalyst for a Cope rearrangement.[65]

1.9 Conformation of Cyclic Hydrazines

The conformation of hydrazines has been studied using both computational and experimental methods. X-ray crystallography is one of the most widely used experimental methods, as it clearly shows the most stable solid-state conformation of a compound. Although this may vary from the lowest energy conformation in solution due to crystal packing effects. Below we report examples of XRD structures across a range of ring sizes, which shows the strong preference for nitrogen substituents to be displayed *anti* to each other.

This has been demonstrated in three previously published studies from the Shipman group[35, 39, 66] which contained solid-state structures of **53**, **75**, **154** and **155** (Figure 1.5). These structures clearly show the strong preference for the substituents on the nitrogens to be orientated *anti* to each other, which can be seen in the large torsion angles between the nitrogen substituents for each example. In addition, each of the nitrogens has a large amount of pyramidalisation,[i] clearly showing unusually high sp^3 character.

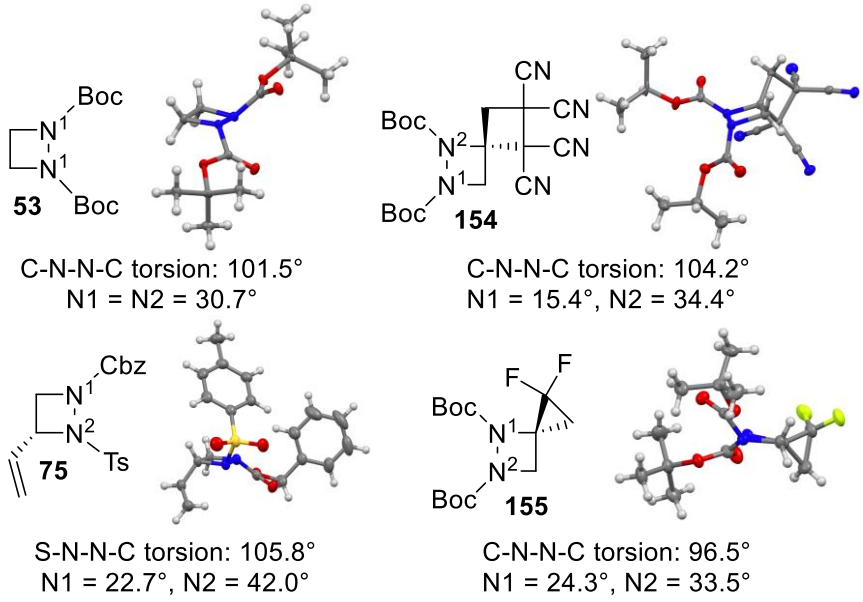


Figure 1.5 Solid-state structures of **53**, **75**, **154** and **155**.[35, 39, 66]

[i] This is 360 ° - [a+b+c], where a, b and c are the angles between the nitrogen substituents. A larger angle indicates more sp^3 character at the nitrogen centre.

These conformational features can also be observed in larger ring sizes. Pyrazolidines **156** and **157** reported by Coldham *et al.*[67] and hexahydropyridazine **158** reported by Greck et al.[53] all show a similar conformational bias in the solid state to the diazetidines, although the extent of pyramidisation is generally lower for the amide nitrogens (Figure 1.6).

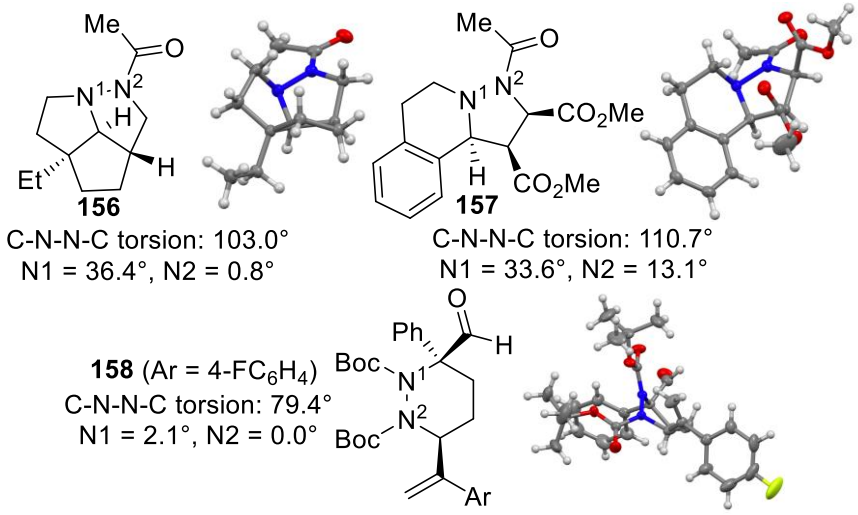


Figure 1.6 Crystal structures of **156**, **157** and **158**.[53, 67]

This is driven partly by the strong preference for substituents to orientate as far from each other as possible, to reduce steric crowding. However, in hydrazines this conformational bias is extremely pronounced because of the nitrogen lone pairs, which to reduce electrostatic repulsion strongly prefer to be *anti* to each other. This has been shown using *ab initio* DFT calculations on hydrazine and related systems by Rauk and Jarvie.[68] They showed that the equilibrium conformation of hydrazine has a dihedral angle of 95° between the nitrogen lone pairs, and that an angle of approximately 90° is optimal for hydrazines **159**, **160** and **161** (Figure 1.7).

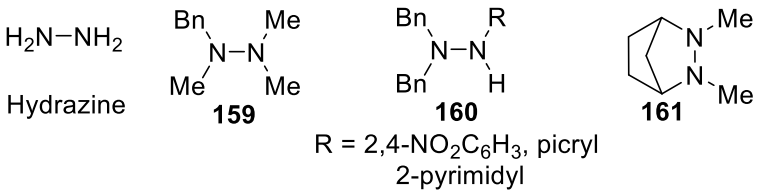


Figure 1.7 Hydrazine compounds analysed using *ab initio* DFT by Rauk and Jarvie.[68]

Rademacher provided further evidence for the strong conformational bias of cyclic hydrazines, he used photoelectron spectroscopy (PE) to measure the dihedral angle between the nitrogen lone pairs of diazetidine **162**, pyrazolidine analogue **163** and hexahydropyridazine analogue **164** for comparison (Figure 1.8).[69] The dihedral angle steadily increased with ring size, which would be expected as larger ring sizes allow for a greater amount of conformational flexibility, allowing the lone pairs to distance themselves further from each other.

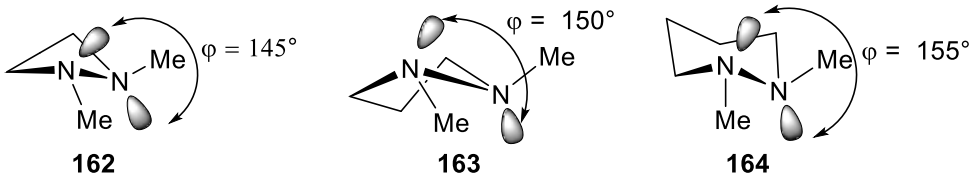


Figure 1.8 Dihedral angles of methyl substituted cyclic hydrazines.[69]

This strong preference can however be overcome in certain cyclic hydrazines. Recent work by Del Valle *et al.* on δ-azaprolines using DFT, X-ray crystallography and NMR showed that **165** has a nitrogen torsion angle of only 10.7° and no observable pyramidisation at either nitrogen (Figure 1.9).[70] This was due to hydrogen bonding between the amine hydrogen and the carbonyl of the acyl substituent, which overcame the hydrazines natural propensity to adopt an *anti,anti* conformation between substituents.

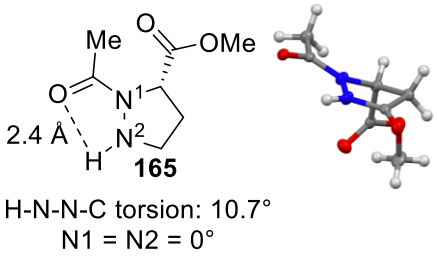


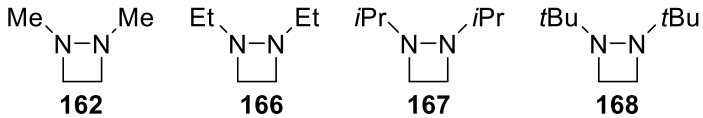
Figure 1.9 Structure of azaproline **165**.[70]

These planar hydrazines structures are also observed in some polycyclic systems like those developed by Kim *et al.*[71] and Pagenkopf *et al.*[72] Apart from these rare exceptions however, cyclic hydrazines adopt a conformation that reduces lone pair repulsion, by placing substituents *anti* to each other.

1.10 Fluxionality of Cyclic Hydrazines

The study of nitrogen inversion within cyclic systems has been studied extensively, and several reviews have been published.[73, 74] It has been shown that there are four main factors that affect the size of inversion barriers: steric effects; conjugation effects, angular constraints and heteroatoms. The barrier to inversion for a system is generally studied by NMR or by computational methods like DFT. Several studies have been conducted into the barriers to inversion of cyclic hydrazines, which have shown that the barriers to inversion are generally high, but fluxional behaviour can often still be observed.

In order to study the effect of substituents on the rate of inversion for diazetidines, Hall and Bigard synthesised **162**, **166**, **167** and **168** (Figure 1.10).[75] They used VT NMR to determine the barrier to inversion for the four substrates and found a strong correlation between the size of the substituent and the magnitude of the barrier to inversion. The observed increase in the barrier to inversion is not linear, with the barrier for *tert*-butyl substituted diazetidine **168** significantly larger than for any other example.



162 68.6 kJ mol^{-1} **166** 69.0 kJ mol^{-1} **167** 70.0 kJ mol^{-1} **168** 85.3 kJ mol^{-1}

Figure 1.10 Diazetidines used to study nitrogen inversion barriers by NMR.[75]

Analysis of the NMR spectra of **162** and **166**-**168** showed a clear AABB coupling pattern for the methylene hydrogens, with a large difference in coupling constant between J_{14} and J_{23} (Figure 1.11). Using the Karplus equation they were able to use this information to calculate that the ring is highly puckered with dihedral angles of 166, 161, 152 and 159° for **162** and **166**-**168** respectively. This means that larger substituents on the nitrogens reduce the substituent torsion angle but not significantly. This also provides further evidence that substituents preferentially oritentate *anti* to each other, although analysis of coupling constants can be more ambiguous than crystallography due to the inherent error in NMR spectrometers and the Karplus equation itself.

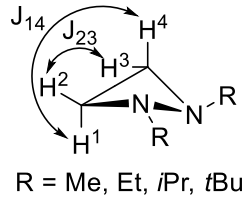


Figure 1.11 Likely orientation of alkyl diazetidines, with a highly puckered ring structure.[75]

Williams *et al.* also studied the barriers to inversion of cyclic hydrazines, however this time they focused on aza-β-lactams – a compound class closely related to diazetidines.[76] The barriers of inversion they reported for these compounds were very high at around 80 kJ mol^{-1} (Figure 1.12). The only exception to this was diphenyl substituted compound **173**, which had a significantly lower barrier of inversion of 54.4 kJ mol^{-1}. This is likely due to the phenyl substituents stabilising the transition state of this inversion process.

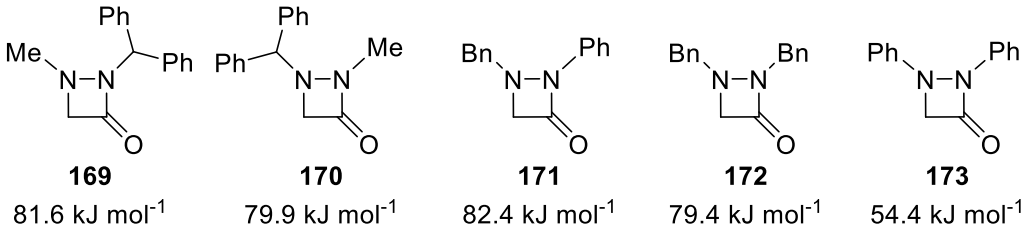


Figure 1.12 Barriers of inversion for a series of closely related aza-β-lactams.[76]

Kostyanovsky *et al.* studied the barrier to inversion for pyrazolidines (Figure 1.13).[77] Compound **175** is the exact homologue of diazetidine **167**, so the barrier to inversion can be directly compared to determine the effect of ring size. The barrier to inversion is 2.3 kJ mol^{-1} lower in the pyrazolidine substrate, showing that increasing ring size will tend to decrease the barrier to inversion. The barrier of inversion for compounds **174** and **176** were also calculated. The barrier for **174** is significantly lower, which is likely due to conjugation of the nitrogen with the carbonyl substituent, which reduces the extent of nitrogen pyramidisation. For substrate **176**, which has a higher barrier, the authors hypothesized that the OH group could plausibly hydrogen bond to one of the nitrogen lone pairs and stabilise the ground state conformation.

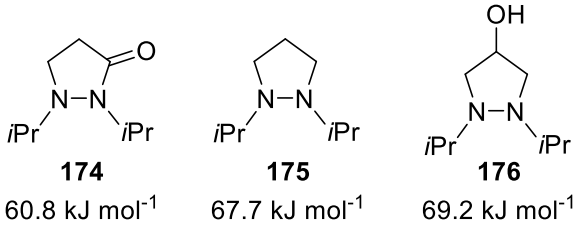


Figure 1.13 Barriers of inversion for a series of pyrazolidines.[77]

Further work by Kostyanovsky *et al.* subsequently analysed other closely related pyrazolidines (Figure 1.14).[78] *tert*-Butyl pyrazolidine **177** was found to exist as a single conformer, the NMR spectra did not show any evidence of other conformers even when heated to 100 °C. Diazetidine **168** only split into multiple conformers when heated to 155 °C so this result fits with the work by Hall and Brigard (Figure 1.10). Similarly, **178**, with methyl groups at C3 and C5 was also extremely stable and did not undergo nitrogen inversion at 100 °C.

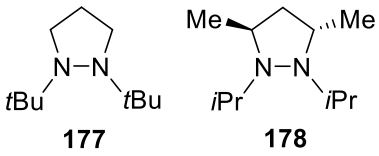


Figure 1.14 Pyrazolidines which did undergo inversion at 100 °C.[78]

Further evidence that the barrier to inversion decreases as ring size increases can be found by comparing diazetidine **162** with hexahydropyridazine analogue **179** studied by Anderson (Figure 1.15).[79] The barrier to inversion for **179** is 48.5 kJ mol^{-1}, is significantly lower than the 68.6 kJ mol^{-1} barrier for **162**, so the increase in ring size lowered the barrier to inversion. **180** and **181** were also studied, deuterated analogue **180** had a slightly higher barrier to inversion, while the addition of methyl substituents at C4 and C5 raised the barrier again for **181**.

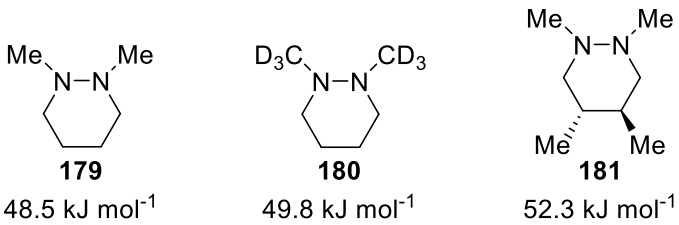


Figure 1.15 Barriers to inversion for hexahydropyridazines **179**-**181**.[79]

Hexahydropyridazine **179** can also be directly compared with dimethyl-cyclohexane **182**, where the methyl groups are *trans* to each other. This compound will also invert from the more stable di-equatorial conformation **185** to di-axial conformation **186**, which is higher in energy due to 1,3-diaxial strain. The corresponding inversion process has a barrier of 11.3 kJ mol^{-1},[80] and this significantly lower barrier than the corresponding barrier for **183** to **184** shows that the adjacent nitrogen's in **179** have a large impact on the barrier to inversion (Figure 1.16).

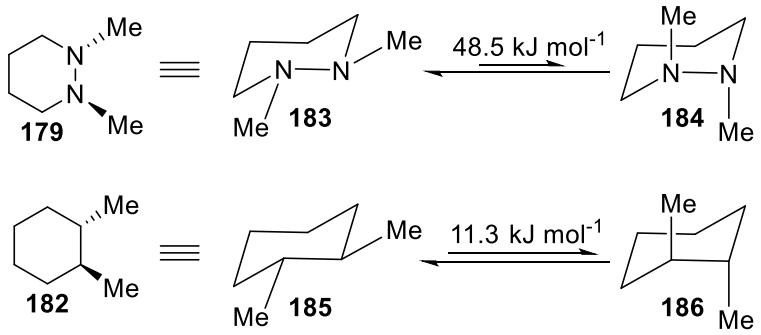


Figure 1.16 Barrier to inversion comparison between **179** and **182**.

The fluxional behaviour of cyclic hydrazines is well documented and the observable trends are similar to those reported in other cyclic systems. Ring size and the size of nitrogen substituents have predictable effects, and the adjacent nitrogens significantly raise the energy required to invert their substituents due to interactions between their lone pairs.

1.11 Research Aims

Whilst there are many excellent examples of syntheses developed for a variety of cyclic hydrazines there is not currently a general methodology that can be applied to the synthesis of multiple cyclic hydrazine ring sizes. This makes the development of diverse cyclic hydrazine libraries challenging, as multiple different synthetic strategies would be required for each ring size. We sought to develop an approach to synthesising cyclic hydrazine scaffolds, with orthogonally protected nitrogen atoms which could then be further diversified using well precedented nitrogen functionalisation chemistry.

We were especially interested in extending this to the development of C3-substituted cyclic hydrazines, as this would not only give access to a further point of diversification but would also influence the orientation of the nitrogen substituents (Figure 1.17). Previous work in the group on **75** (Figure 1.5), had shown that adding a substituent at the C3 position of a diazetidine enantioselectively enforces the *anti,anti* conformation in the solid state. We wanted to test whether this conformation is favoured for cyclic hydrazines with different ring sizes and substituents (**187**) in order to to see if this is a general feature of this class of compounds.

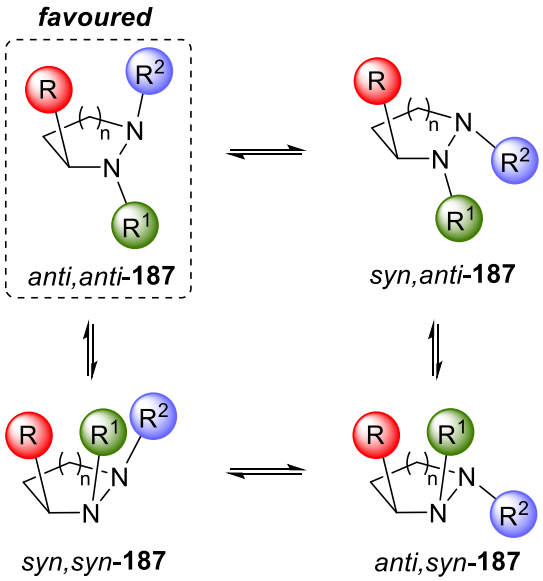


Figure 1.17 Proposed orientation of cyclic hydrazine scaffold **187** with a C3 substituent.

We envisioned that these compounds would be interesting for medicinal chemistry as sp^3-rich, heterocyclic and non-planar frameworks. They would also effectively contain three stereogenic centres despite only requiring a single enantioselective transformation during their synthesis, as the orientation of the nitrogen substituents is determined by the C3 substituent. We also wanted to study the dynamic behaviour of these systems in solution, by determining whether inversion of the nitrogen substituents can occur and if so, how high the barrier to inversion might be.

To synthesise these cyclic hydrazines we would need to synthesise orthogonally protected precursor **188**, which could then be functionalised

iteratively to give **187** (Figure 1.18). We wanted to use a ring closure strategy to synthesise **188** from **189**, as the same cycloaddition methodologies cannot be applied to multiple ring sizes. Compound **189** could be synthesised by adding hydrazine **191** to a precursor like **190**, however, enantioselective installation of leaving group X is likely to be the most significant challenge to this strategy.

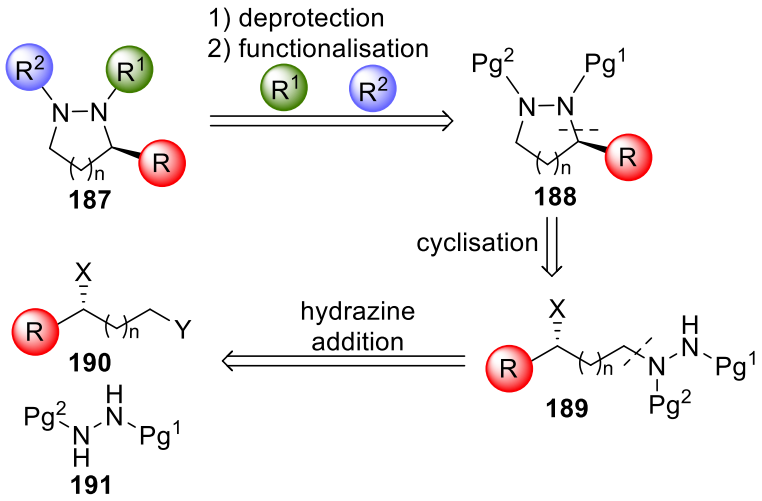


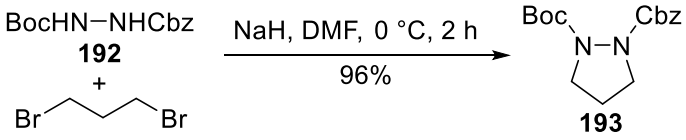
Figure 1.18 Retrosynthetic analysis of target **187**.

In the special case where R = H the synthetic challenge is significantly simplified, as an enantioselective methodology is not required. This would still generate a hydrazine scaffold with two points for diversification and would also allow optimisation of the ring closing and functionalisation steps. This is where we decided to begin our research, with a view to developing an enantioselective methodology once this had been optimised.

Chapter 2: Synthesis of Cyclic Hydrazines

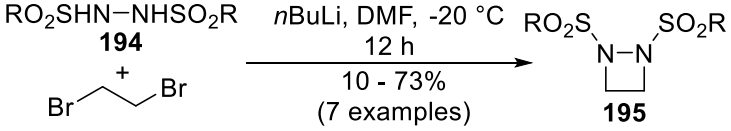
2.1 Synthesis of Orthogonally Protected Diazetidines

Our initial focus was the synthesis of diazetidines, which would have two points of diversity *via* functionalisation of the nitrogen atoms. Although these were likely to be synthetically challenging compounds to synthesise (in comparison with larger ring sizes) this would provide us a good opportunity to develop a robust synthetic method and would also give us access to unusual scaffolds. Additionally, the synthesis of orthogonally protected pyrazolidines is already well precedented, for example the synthesis of **193** by Sherrill (Scheme 2.1).[81]



Scheme 2.1 Synthesis of pyrazolidine **193** by Sherrill.[81]

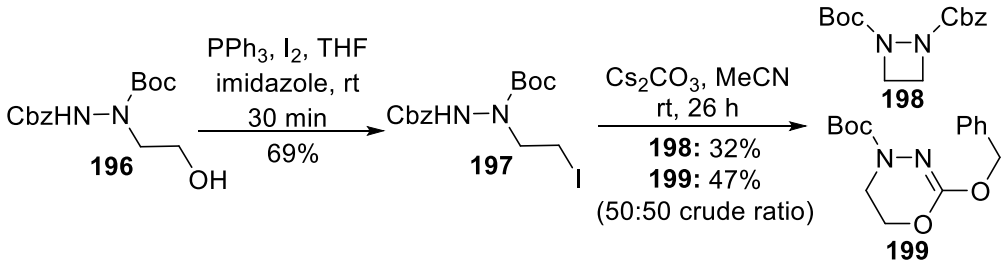
There is no precedent that we are aware of for the synthesis of orthogonally protected diazetidines. Work reported previously in the group has shown it is possible to synthesis diazetidines with two identical protecting groups (Scheme 1.14). The condensation of 1,2-disulphonylhydrazines with 1,2-dibromoethane to give diazetidines **195** was reported by Cui *et al.* (Scheme 2.2).[83] However this is not compatible with carbamate protecting groups or orthogonally protected hydrazines so we needed to develop a different approach.



Scheme 2.2 Synthesis of sulphonyl functionalised diazetidines **196**.[83]

Initially we targeted Cbz/Boc protected system **196**, as both protecting groups are orthogonal and there are a large number of methods available for their removal.[82] This would also be analogous to pyrazolidine **193** and similar to **53**

(Scheme 1.14), although a different synthetic strategy would be required. Using the synthesis of orthogonally protected linear hydrazides developed by Licandro *et al.*[84] we synthesised protected hydrazine **196** from 2-hydroxyethylhydrazine (Scheme 2.3). This was converted to iodide **197** in good yield; however, the cyclisation generated a mixture of diazetidine **198** and the undesired oxadiazine **199** in a 50:50 crude ratio (by ^{1}H NMR). Isolation of diazetidine **198** proved challenging owing to its similar polarity to oxadiazine **199**, and it was only isolated in a modest yield of 32%.



Scheme 2.3 Synthesis of Cbz/Boc protected diazetidine **194**.

This was not unexpected as earlier work group had shown that this issue occurred with carbamate protected diazetidine precursors (Scheme 1.14).[35] The use of the Mitsunobu reaction on substrates similar to **196** was found to exclusively generate the oxadiazine, so this method was not attempted on substrate **196**. A crystal structure of **198** was obtained to unambiguously determine that the desired diazetidine was synthesised (Figure 2.1). This had similar parameters to **53**, which had two Boc groups, although the torsion angle and nitrogen pyramidisation values are slightly smaller.

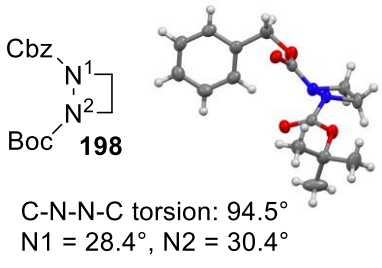
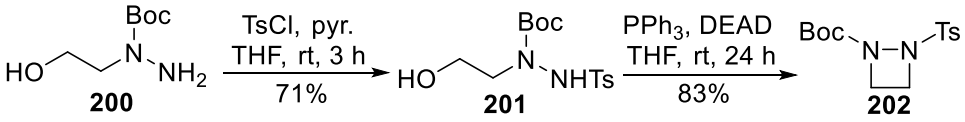


Figure 2.1 Crystal structure of **198**.

In order to improve the synthesis we decided to attempt an alternative ring closure strategy, replacing the Cbz group with a Ts group, as this had previously

been shown to be a superior protecting group for the cyclisation.[35] This synthesis proved to be much more efficient (Scheme 2.4), and was completed to give diazetidine **202** in an overall yield of 58% in only two steps. Not only does this require one less step than the synthesis of **198**, but the overall yield of that process was only 22%. The purification after cyclisation by chromatography was also much simpler as diazetidine **202** is the major product.

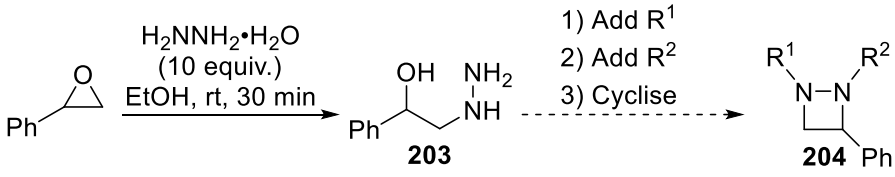


Scheme 2.4 Synthesis of Ts/Boc protected diazetidine **202**.

2.2 Synthesis of C3-Substituted Diazetidines from Epoxides

Next, we turned our attention to the synthesis of diazetidines which have C3 substituents. This extra substituent would greatly improve library diversity. In addition it was expected to control the stereochemistry at all three substituents. This assertion is based on the previous synthesis of **75** in the group, which had shown the strong conformational bias for *anti*,*anti* substituents (Figure 1.5).

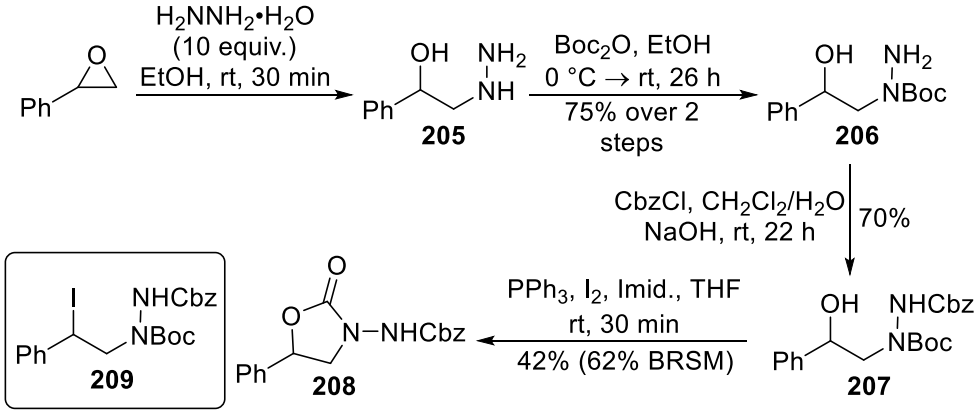
As these compounds would have a stereocentre at C3, the synthesis was likely to be significantly more challenging. Initially, we used racemic styrene oxide to find a reliable method for the synthesis of the target. Our proposed approach was to open the epoxide ring using hydrazine monohydrate to generate **203**, which had been previously reported by White *et al.*[85] We then envisioned that this substrate could be sequentially functionalised with orthogonal protecting groups and cyclised in a similar manner to the unsubstituted system to give diazetidine **204** (Scheme 2.5).



Scheme 2.5 Proposed synthetic strategy for diazetidine **204**.

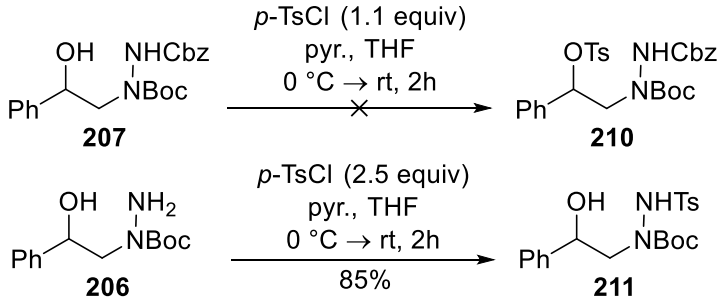
This proposed route had several potential benefits, it would be a short synthesis that exploits chemistry we had already developed (Scheme 2.3 and 2.4). In addition, there are a large number of strategies for enantioselective epoxide synthesis with excellent yields and selectivity, including Jacobsen's kinetic resolution[86] and Jacobsen-Katsuki epoxidation.[87, 88] It did however have some potential drawbacks, including the use of hydrazine monohydrate – which is a hazardous reagent and is also prone to explosive decomposition when heated.[89] The published ring opening also required the use of ten equivalents of hydrazine monohydrate and was an exothermic process.

We began exploring the synthesis of C3-phenyl substituted diazetidines using *rac*-styrene oxide. The ring opening and subsequent Boc protection was successful (Scheme 2.6), although the Boc protection proved significantly more challenging than for 2-hydroxyethylhydrazine, which we used to synthesise **200**. This was because isolation of hydrazinyl alcohol **205** from the excess hydrazine monohydrate used in the reaction was challenging and performing the Boc protection on the crude mixture complicated purification. Kugelrohr distillation proved to be the most effective method of removing the excess hydrazine monohydrate. Purification of **206** by recrystallisation from toluene was effective but the isolated yield was only 45%. Purification by flash chromatography gave material with minor impurities but the yield could be significantly improved to 75% and this material was of sufficient purity for subsequent transformations. Cbz protection of the other nitrogen was also successful, giving **207** with a yield of 70%. Attempts to convert the alcohol to the iodide were not successful, as subjecting the precursor to iodination conditions caused cyclisation to the undesired oxazolidinyl carbamate **208**, instead of iodide **209**.



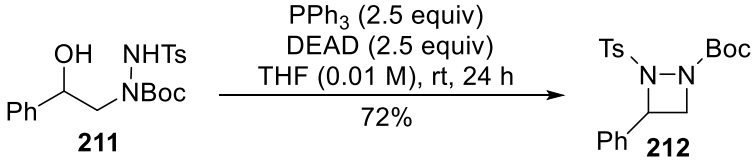
Scheme 2.6 Attempted synthesis of **209**, which gave **208**.

Next, we attempted to form the tosylate as an alternative leaving group. Tosylation was attempted on both the fully protected **207** and Boc protected amine **206** (Scheme 2.7), however, neither approach was successful, although in the second case tosylation on the nitrogen gave **211**.



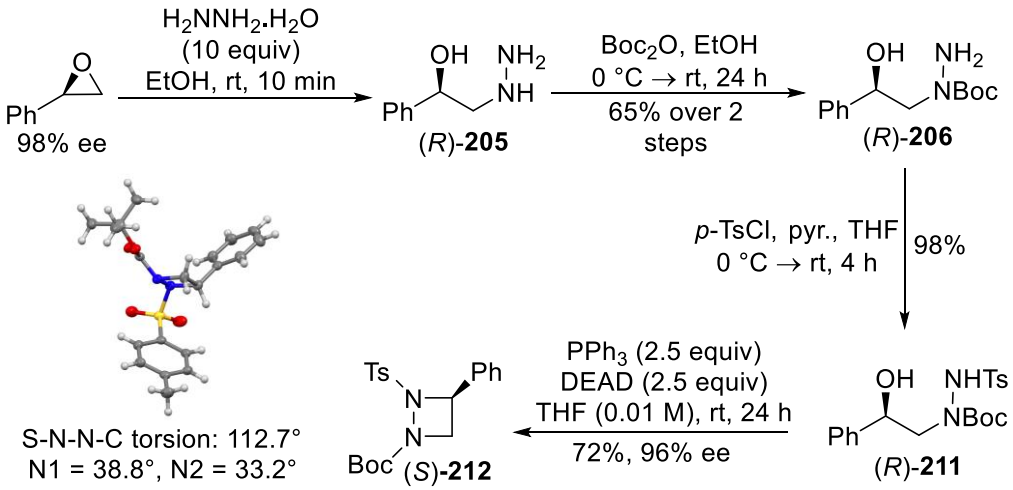
Scheme 2.7 Attempted tosylation reactions.

We solved this by using **211**, which could be converted directly to diazetidine **212** using the Mitsunobu reaction in a 72% yield (Scheme 2.8). To achieve optimal conversion to the product, highly dilute conditions (0.01 M THF), and an excess of both DEAD and PPh_3 (2.5 equiv each) were needed, these conditions together gave an isolated yield of 72%.



Scheme 2.8 Successful synthesis of racemic diazetidine **212** *via* the Mitsunobu reaction.

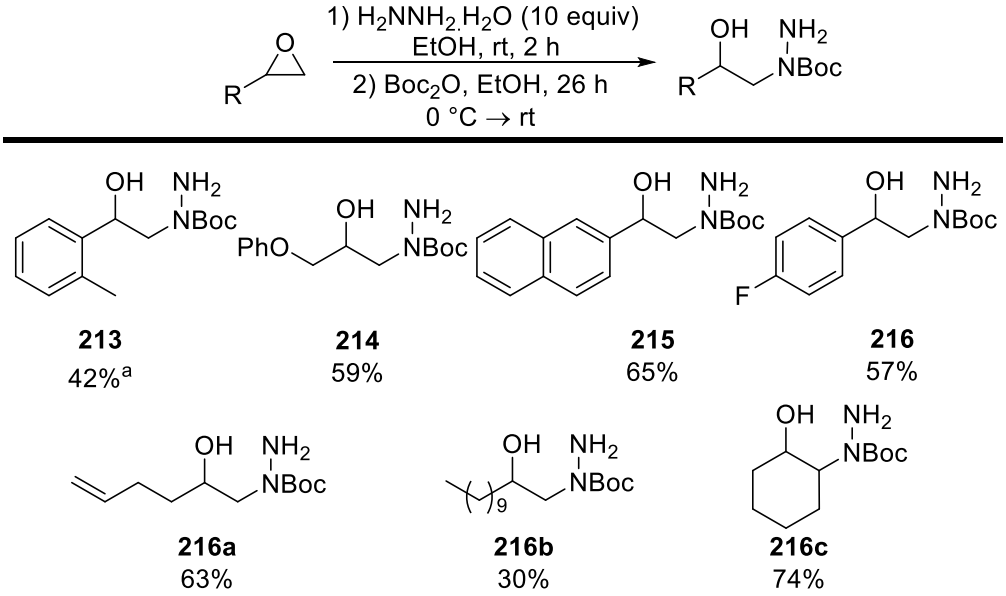
After this initial success, we repeated the synthesis with commercially available (*R*)-phenyloxirane which had an ee of 98% as measured by chiral HPLC (Scheme 2.9). Analysis by chiral HPLC of (*S*)-**212** confirmed that no significant racemisation occurred during the sequence which was completed in an overall yield of 46% over the four steps. The yields were almost identical to those obtained in the racemic synthesis as expected. In order to unambiguously determine the structure and expected stereochemistry of (*S*)-**212** we also obtained a crystal structure. The Flack parameter obtained for this structure was 0.016(11), which is small and with a small associated error, meaning we can have a high degree of confidence that the stereocentre is *S*. This also showed that in the solid state the nitrogen substituents adopt an *anti*,*anti* conformation, as in vinyl diazetidine **75**. Observed torsions and nitrogen pyramidisations were also similar (Figure 1.5).



Scheme 2.9 Synthesis of (*S*)-**212** from (*R*)-phenyloxirane.

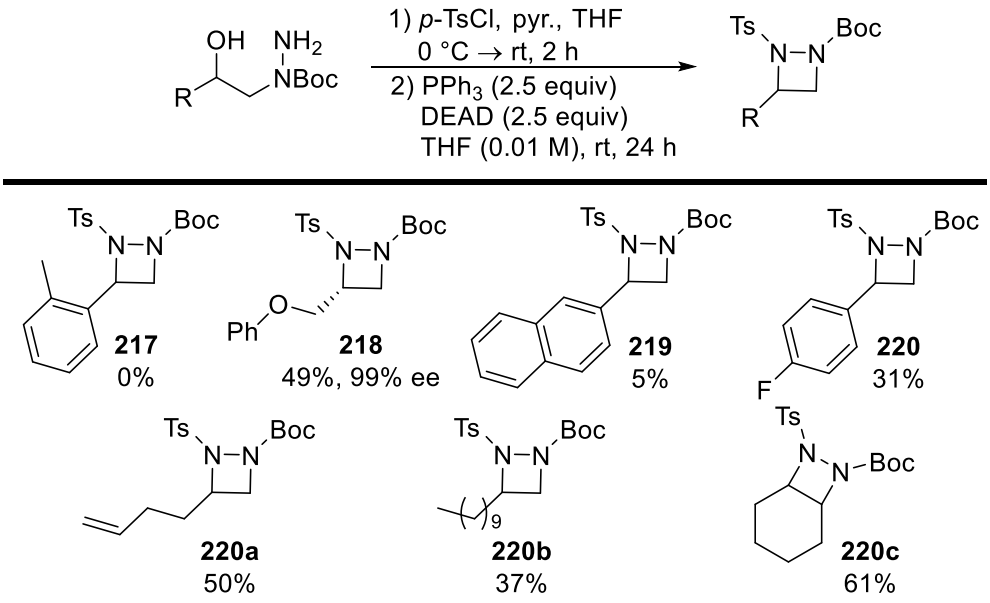
After this success we attempted to explore the scope of this synthetic route by varying the substituent at the C3, which was achieved by varying the starting epoxide. Initially racemic epoxides were used as these are all commercially available. The ring opening of the epoxide and Boc protection proved to vary somewhat in yield for each of the seven substrates tested, with yields ranging from 74% for cyclohexyl substituted **216c** down to 30% for decyl substituted **216b** (Scheme 2.10). We were pleased to note however that this methodology

tolerated a wide range of aryl and alkyl functional groups across the seven examples that we tested.



Scheme 2.10 Synthesis of **213**-**216c**.

The tosylation and cyclisation was unexpectedly difficult for some substrates (Scheme 2.11). For the *o*-tolyl substituted compound **213** the tosylation was unsuccessful despite multiple attempts, although there is no obvious reason why this substrate should be particularly challenging. For naphthyl substituted **219**, the yield of both the Ts protection and cyclisation were low (16% and 31% respectively), which was likely due to poor solubility. This made purification by chromatography challenging; recrystallisation may have been a better purification method but there was insufficient material to attempt this. The synthesis of the glycidyl phenyl ether substituted diazetidine **218** was subsequently completed using the (*R*)-epoxide, and the (*S*)-**218** diazetidine showed no evidence of racemisation when analysed by chiral HPLC, with 99% ee for both the epoxide and the resultant diazetidine. Alkyl substituted diazetidines **220a-c** were also isolated in moderate yields over the two-step process, which makes this a complementary methodology to our subsequent ATH work (*vide infra*) which was effective for aryl substituted diazetidines.



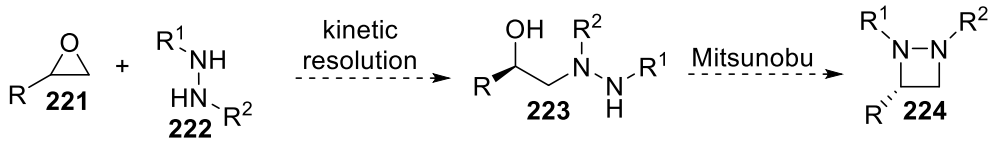
Scheme 2.11 Scope of bisprotected hydrazines *via* Ts protection and cyclisation.

Although we had developed a route to several C3-substituted diazetidines and shown that the sequence is stereospecific, the synthetic route had several drawbacks. The product from the Boc protection step was challenging to purify, which resulted in reproducibility issues. In addition, the ring opening step required ten equivalents of hydrazide monohydrate, which is both hazardous and prone to explosive decomposition, so substituting it was a priority. Finally, the synthesis required four steps, which makes the overall process time consuming with multiple purifications. Despite this the synthesis of (*S*)-**212** and (*S*)-**218** were both completed on gram scale.

2.3 Attempted Hydrazinyl Kinetic Resolution Using Jacobsen's Catalyst

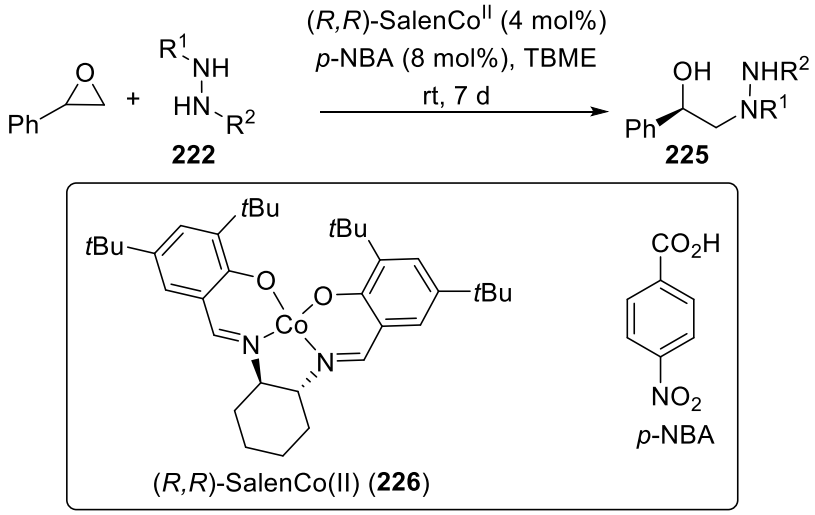
We decided to explore an alternative method to open the epoxide which would potentially generate the diazetidines in higher yields and fewer steps while also removing the need to use hydrazide monohydrate. We initially considered Jacobsen's catalyst and fully protected hydrazide **222** to open epoxide **221**, which would allow us to isolate enantiopure linear hydrazine precursors **223** from racemic epoxides (Scheme 2.12). These could then by cyclised to diazetidines **224** in the same manner as **212**. Bajaj *et al.*,[90, 91] had previously shown that aminolytic kinetic resolution (AKR) could be done with

protected amines, and so it seemed plausible the reaction might tolerate protected hydrazides.



Scheme 2.12 Proposed 2-step synthesis of diazetidines using kinetic resolution.

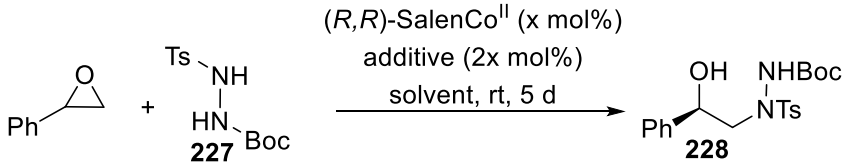
Initially we used conditions reported by Bajaj *et al.*,[91] which used Jacobsen's catalyst (*R*,*R*)-SalenCo^{II} (**226**),[92] with six different hydrazides (Table 2.1). The use of hydrazine monohydrate (entry 1) was unsuccessful, which was likely due to its high reactivity. *tert*-Butyl carbazate (entry 2) was more promising, with the desired compound detected by LCMS, however even after seven days the reaction was incomplete. Furthermore, it was not possible to determine the ratio of product to starting material using NMR or HPLC. The use of Ts/Boc protected hydrazide was the most promising (entry 6), although again the reaction was not complete. The reaction was readily monitored by NMR as the regioisomer of the expected product **211** had already been synthesised, and signals in approximately the correct places could be clearly seen in the ^{1}H NMR of the crude reaction mixture.



Reaction	R^1	R^2	Result
1	H	H	Complex mixture
2	H	Boc	Incomplete
3	H	Ts	No reaction
4	Boc	Boc	No reaction
5	Ts	Ts	No reaction
6	Ts	Boc	1:1 SM:P (by ^{1}H NMR)

Table 2.1 Optimisation of the kinetic resolution using different hydrazides.

After this promising initial result we attempted to find better conditions that would accelerate the rate of reaction (Table 2.2), however, changing either solvent, additive, or temperature either slowed the rate of reaction or stopped the reaction entirely. Increasing catalyst loading from 4 to 10 mol% (entry 8) did provide modest improvements but did not give complete conversion.



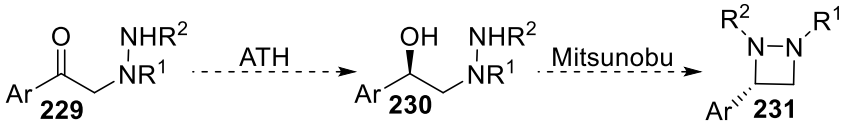
Entry	Solvent	Additive	x	Result (by ^{1}H NMR)
1	CH_2Cl_2	*p*-NBA	4	Trace amount of product
2	THF	*p*-NBA	4	4:1 ratio of SM:P
3	*i*PrOH	*p*-NBA	4	7:1 ratio of SM:P
4	THF	TFA	4	No reaction
5	THF	Oxalic acid	4	No reaction
6	THF	*p*-NBA	10	2.5:1 ratio of SM:P
7[a]	THF	*p*-NBA	4	9:1 ratio of SM:P

Table 2.2 Solvent and additive screen for the kinetic resolution. [a]Reaction run at 40 °C

Although some of the results obtained showed the transformation is occuring, the reaction was too slow (under all conditions) to be synthetically useful. The reason for the sluggish reactivity was not clear; it is possible the hydrazide substrates were binding to the catalyst and deactivating it, preventing sufficient catalyst turnover to drive the reaction to completion. Ultimately, we decided to attempt no further optimisation, and instead to explore alternative synthetic strategies.

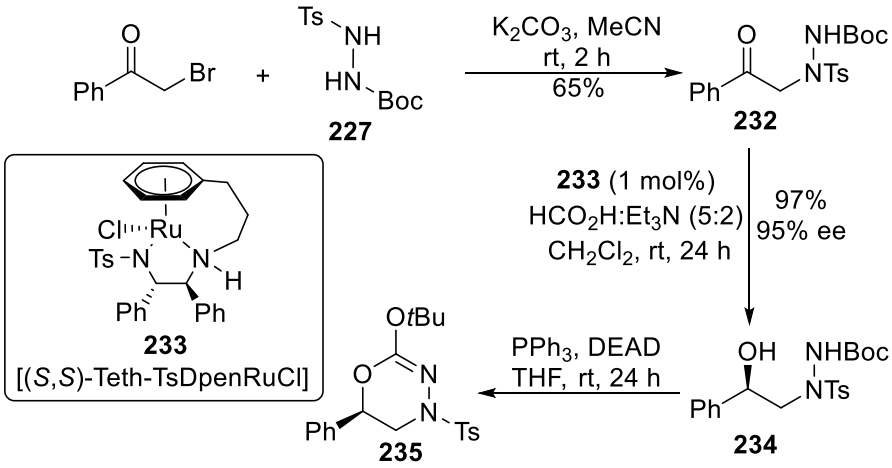
2.4 Synthesis of Diazetidines Using ATH

The next strategy that we explored was asymmetric transfer hydrogenation (ATH), which would allow the synthesis of diazetidines from protected keto hydrazides **229** (Scheme 2.13). This would be converted to give alcohol **230** using ATH, similar to those from the epoxide opening work. Ring closure using the Mitsunobu reaction would generate diazetidine **231**.



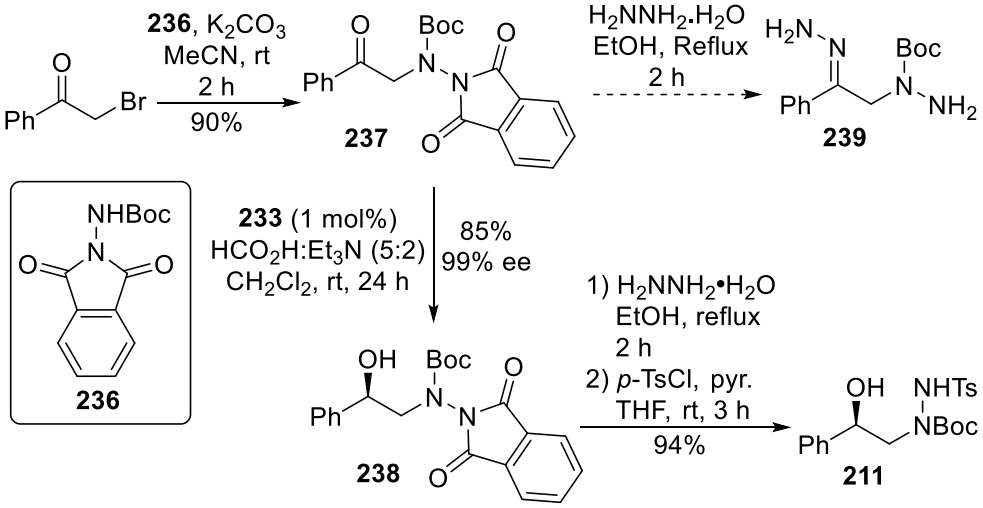
Scheme 2.13 Proposed synthesis of **231** with ATH as the key step.

Early studies were conducted by Dr Rajkumar Sundaram but are included here to provide context. Initial attempts used hydrazine **227**, with a Boc group and a Ts group (Scheme 2.14).[39] We reasoned that the more acidic NHTs group would be deprotonated and thus would provide regioselectivity. This proved to be the case in the initial alkylation reaction with 2-bromoacetophenone to give **232**; however, the cyclisation exclusively generated oxadiazine **235**. This was not unexpected as it had been observed when similar substrates were used in the group.[35] Although this strategy was not successful, we were very encouraged by the efficacy of the ATH reaction in the synthesis of alcohol **234**, utilising catalyst **233** developed by the Wills group.[93]



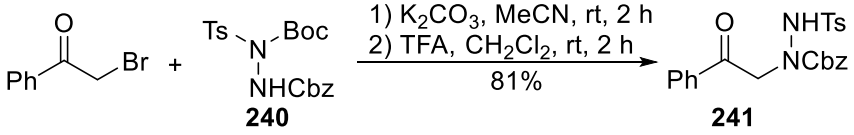
Scheme 2.14 Synthesis of dihyrooxirane **235**. Completed by Dr Rajkumar Sundaram.

In order to achieve ring closure to the desired diazetidine we needed the Ts group to be on the terminal nitrogen. One way to achieve this was to use hydrazine **236** with a phthalimide and Boc group (Scheme 2.15).[94] As the phthalimide protected nitrogen is not nucleophilic the Boc protected nitrogen preferentially reacts with the bromo ketone. Substrate **237** was then converted to alcohol **238** using catalyst **233**, which could then be converted to alcohol **211** after exchange of the protecting groups. Attempts to remove the phthalimide group prior to the ATH reaction were unsuccessful, forming a by-product that appeared to be hydrazone **239** from the ^{1}H NMR of the crude reaction mixture. The deprotection of the phthalimide group again required the use of hydrazine monohydrate, however this can be removed with an aqueous workup, so using it here is less problematic than in our previous work (Scheme 2.6).



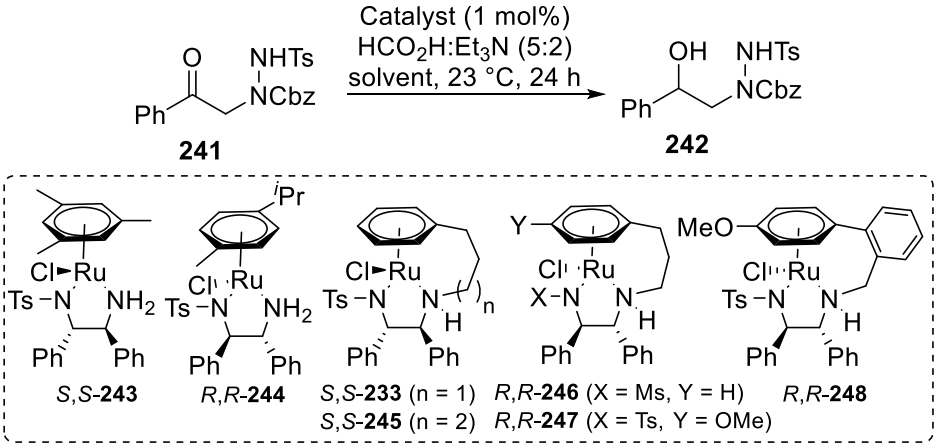
Scheme 2.15 Synthesis of alcohol **211** using protected hydrazine **236**.

We also investigated an alternative approach using a hydrazine with three orthogonal protecting groups **240**.[95] Alkylation of 2-bromoacetophenone with **240** followed by removal of the Boc group generated keto hydrazide **241** (Scheme 2.16). This strategy was better than the phthalimide synthesis above as it introduces the key ATH step later in the synthesis, so less of the valuable chiral material is wasted. It also obviates the need to use hydrazine monohydrate in large excess.



Scheme 2.16 Synthesis of keto hydrazide **241**. Completed by Dr Rajkumar Sundaram.

With ketone **241** synthesised we next optimised the ATH reaction (Table 2.3). Seven different ATH catalysts were tested, with the catalysts from the Wills group giving the best results. Catalyst (*S*,*S*)-**233** was the most effective (entry 3). It was most efficient when dichloromethane was used as the solvent.



Entry	Catalyst	Solvent	Yield [%][a]	ee [%][b]
1	*S*,*S*-**243**	CH_2Cl_2	86	97 (*R*)
2	*R*,*R*-**244**	CH_2Cl_2	16[c]	91 (*S*)
3	*S*,*S*-**233**	CH_2Cl_2	97	99 (*R*)
4	*S*,*S*-**245**	CH_2Cl_2	7	97 (*R*)
5	*R*,*R*-**246**	CH_2Cl_2	97	97 (*S*)
6	*R*,*R*-**247**	CH_2Cl_2	80	99 (*S*)
7	*R*,*R*-**248**	CH_2Cl_2	16	98 (*S*)
8	*S*,*S*-**233**	$CHCl_3$	96	99 (*R*)
9	*S*,*S*-**233**	EtOAc	88	99 (*R*)
10	*S*,*S*-**233**	MeCN[d]	66	98 (*R*)
11	*S*,*S*-**233**	MeOH[e]	92	99 (*R*)

[a]Isolated yield after column chromatography. [b]ee determined by HPLC analysis using chiralpak ADH. [c]Reaction run for 48 h. [d]Reaction run at 0.3 M. [e]Reaction run at 0.2 M.

Table 2.3 Optimisation of the ATH. Completed by Dr Rajkumar Sundaram.

We were able to unambiguously confirm the structure and absolute configuration of alcohol **242** by X-ray crystallography (Figure 2.2). The

observed stereochemistry is consistent with previous work in the Wills group using catalyst (*S*,*S*)-**233**.[93] They have previously hypothesised that catalyst binding is mainly influenced by a favourable CH/π interaction, so the observed sense of asymmetric induction which follows this expected model confirms that the hydrazine group is not disrupting this binding model.

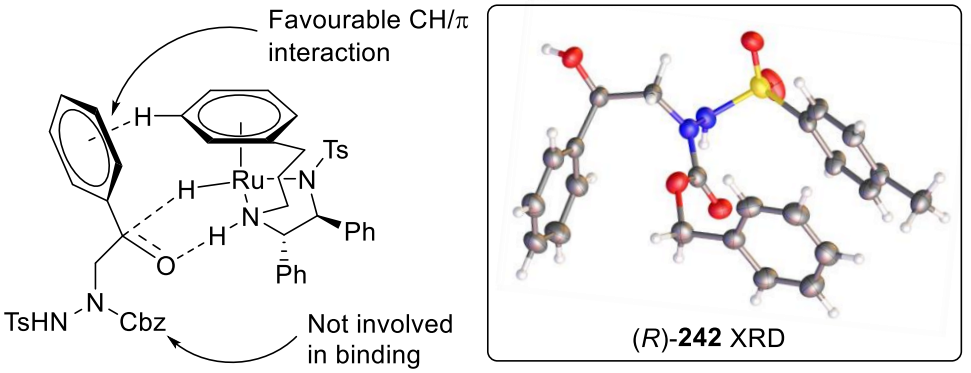
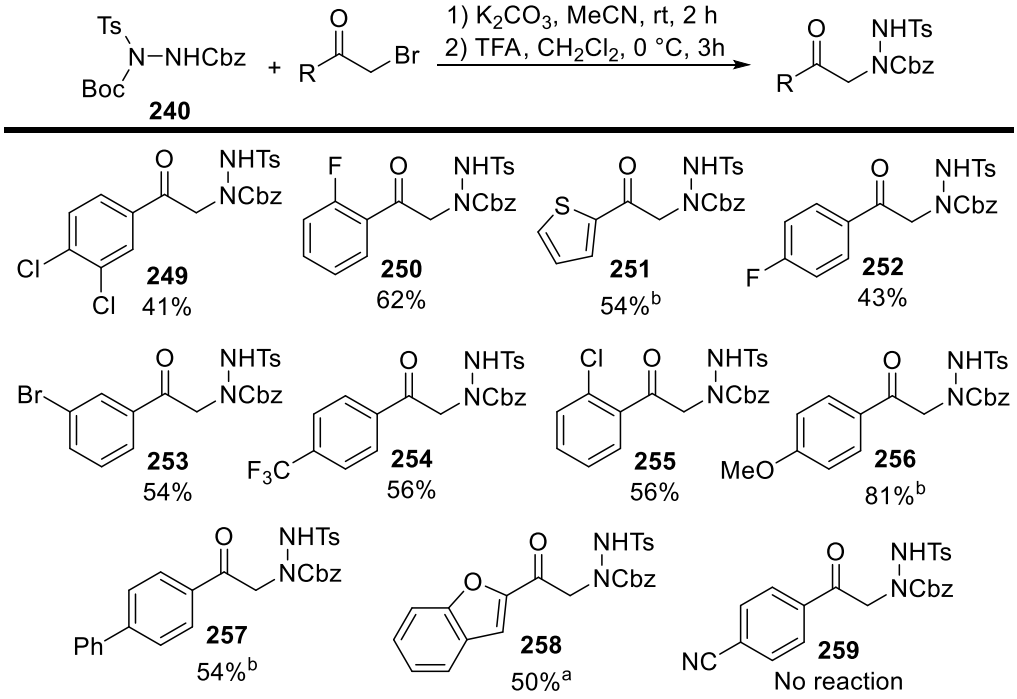


Figure 2.2 Proposed catalyst binding and XRD of (*R*)-**242**, by Dr Rajkumar Sundaram.

2.5 Scope of the Diazetidine Synthesis

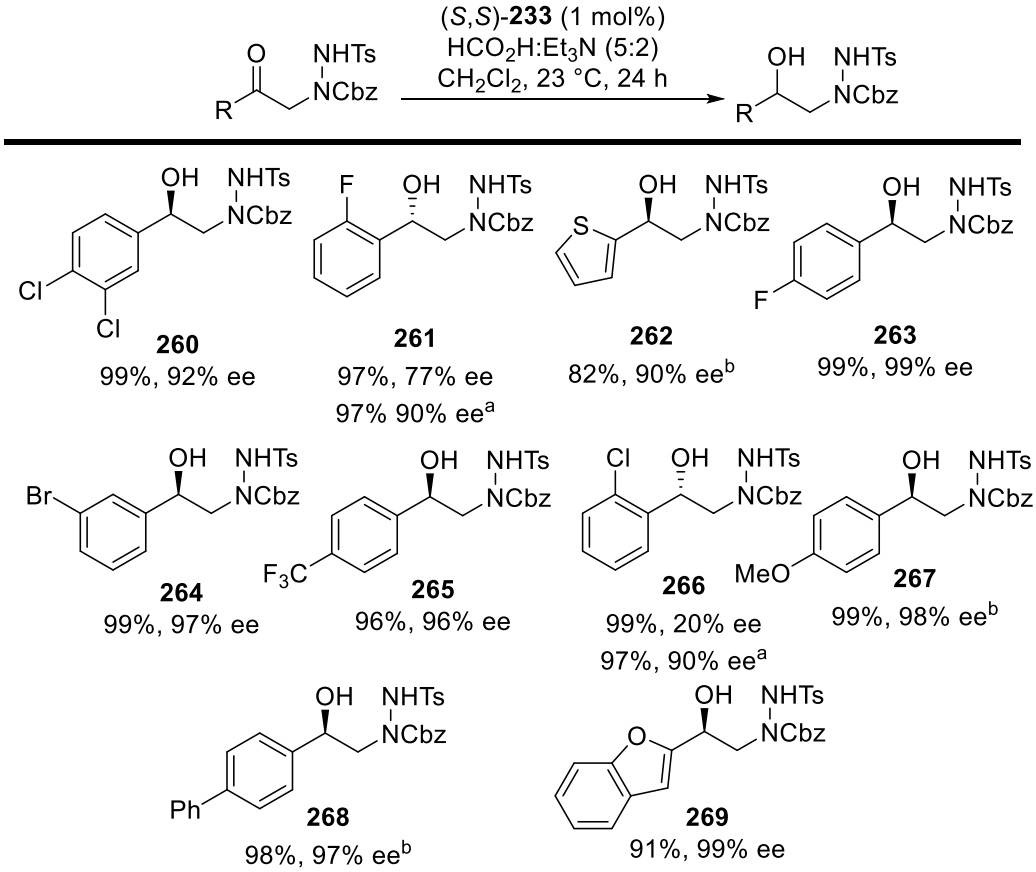
At this point, I largely took over the work of Dr Rajkumar Sundaram and we explored the scope of the diazetidine synthesis. We started by using a variety of aryl ketones, which were commercially available. The synthesis of the keto hydrazides was shown to be tolerant of a wide variety of aryl groups, including heteroaryl substituents (Scheme 2.17). The yields were generally quite modest for the 2-step process, with only the *p*-methoxy (**256**) compound giving a high yield. These lower yields were due to the formation of a small amount of a by-product during the Boc deprotection, which we were unable to isolate. In order to remove it the substrates had to be recrystallised which led to material loss. The deprotection of benzofuran **258** was completed with HCl in dioxane as TFA lead to decomposition of the product.



Scheme 2.17 Synthesis of keto hydrazide precursors. [a]Boc deprotection completed using 2 M HCl in dioxane. [b]Synthesised by Dr Rajkumar Sundaram.

With these compounds in hand the scope of the ATH reaction was explored (Scheme 2.18). Most substrates performed extremely well using (*S*,*S*)-**233**, the only exception proved to be *ortho*-substituted derivatives. These still gave the required alcohols in excellent yields, however the enantioselectivity for the ATH was significantly lower, perhaps suggesting these substrates are coordinating less effectively to the ketone. This was improved by changing to (*R*,*R*)-**247** with a *para*-methoxy substituent, which has previously been shown to be more effective for *ortho*-substituted substrates.[96] This provided a significant increase in enantioselectivity, especially for the *ortho*-chloro substrate **266**.[ii]

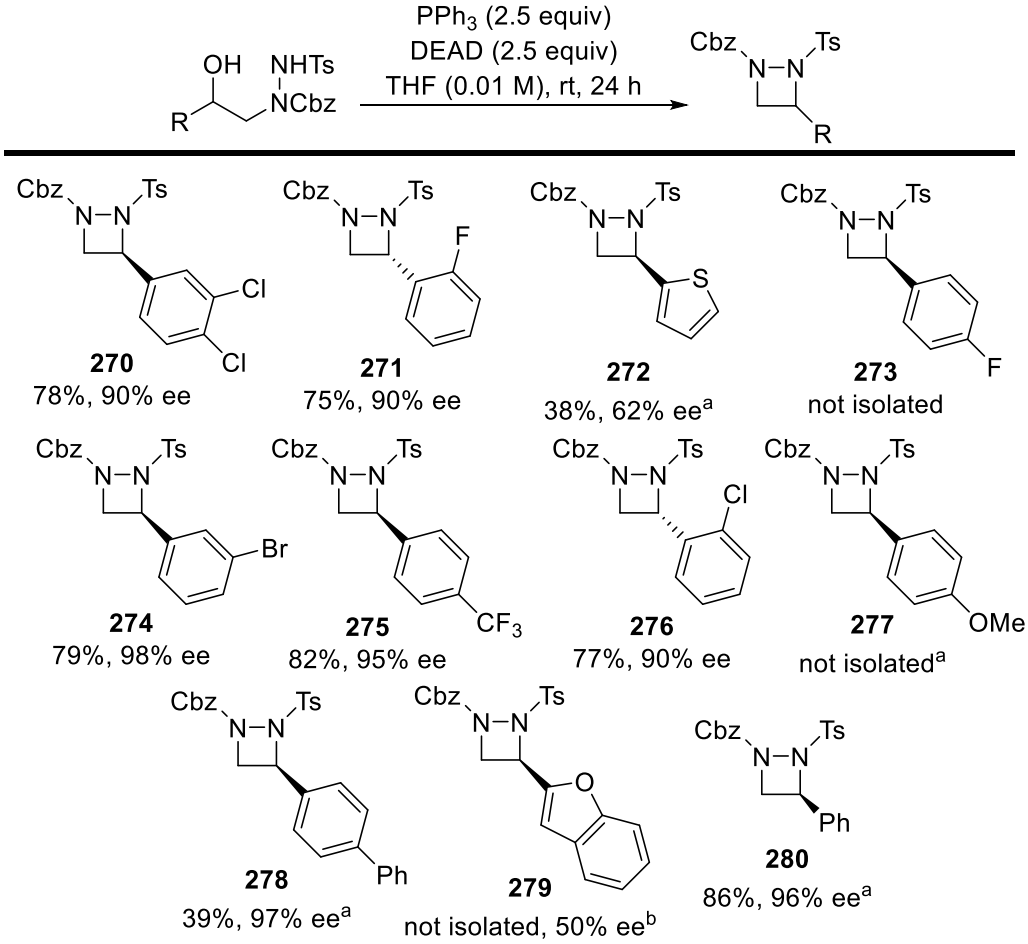
[ii] In order to determine ee, two different methods were used. Either the opposite enantiomer of each compound was synthesised using the opposite catalyst enantiomer i.e. (*R*,*R*)-**233** instead of (*S*,*S*)-**233**. Alternatively, the substrate was reduced using sodium borohydride in methanol to generate an authentic racemic sample for comparison using chiral HPLC. See experimental section for details.



Scheme 2.18 Scope of the ATH reaction. [a]Catalyst (*R*,*R*)-**247** used. [b]Synthesised by Dr Rajkumar Sundaram.

The cyclisation reaction proved more challenging (Scheme 2.19). Three substrates, benzofuran **279**, 4-methoxy **277** and 4-fluoro **273**, proved difficult to isolate due to the presence of a by-product which could not be removed using column chromatography. Further purification and optimisation was not attempted. There was also significant variation in the yield for the cyclisation, in general the substrates with halogens on the aromatic ring (with the exception of 4-fluoro **273**) were the most successful, while other substrates, (thiophene **272**, biphenyl **278**, and phenyl **280**) were only isolated in moderate yields.[iii]

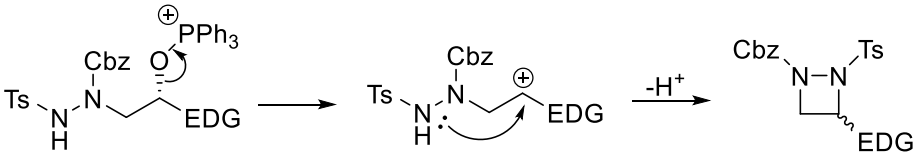
[iii] The ee was determined either by synthesising both enantiomers and mixing or by synthesising the racemate and using this as a standard for chiral HPLC. See experimental section for further details.



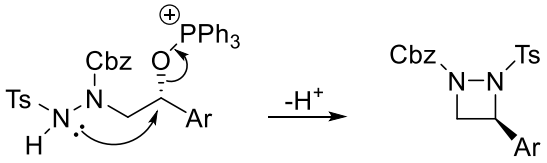
Scheme 2.19 Scope of the Mitsunobu reaction for diazetidines. [a]Synthesised by Dr Rajkumar Sundaram. [b]ee estimated using chiral HPLC

In addition, the thiophene (**272**) and benzofuran (**279**) substituted compounds racemised significantly during the cyclisation process. All these substrates have strongly electron donating substituents, which would stabilise the carbocation formed in an S_N1 reaction (Scheme 2.20). The other substrates in Scheme 2.19 are not strongly electron donating, and are unable to stabilise a carbocation, thus they presumably react exclusively *via* a unimolecular S_N2-type reaction.

S_N1 (*EDG = electron donating group,* **272** and **279**):

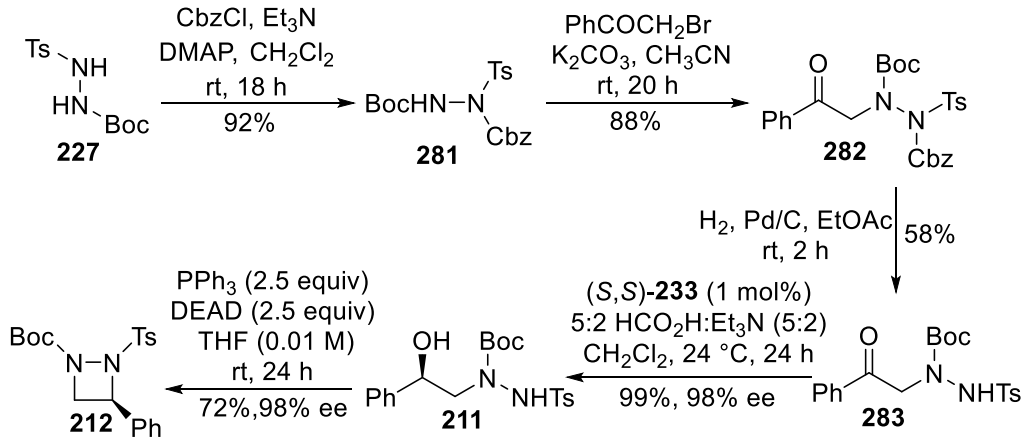


Unimolecular S_N2-type (*for neutral, electron withdrawing Ar groups*):



Scheme 2.20 Proposed rationale for racemisation in the Mitsunobu reaction.

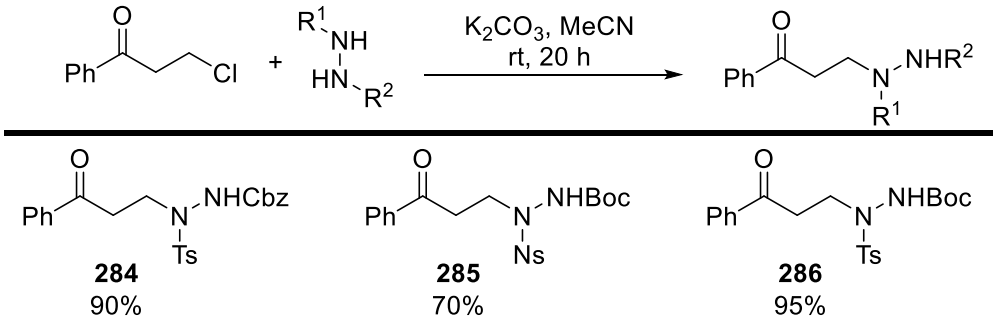
Next, diazetidines containing Boc rather than Cbz groups were targeted, which was achieved by using triply protected hydrazine **281** (Scheme 2.21). This was synthesised in a similar manner to **240**,[95] and then converted to keto hydrazide **282**. The most challenging step proved to be the removal of the Cbz group by hydrogenation with palladium on carbon. **283** was susceptible to further reduction to *rac*-**211**, which is surprising as aryl ketones are usually stable to hydrogenation with palladium. Reducing the reaction time to 2 h minimised the production of *rac*-**211** while ensuring full conversion of **282** to **283**, however in order to remove traces of *rac*-**211** prior to the ATH, the material needed to be recrystallised reducing the yield. Overall however, this sequence was lower yielding (33% over 5 steps) than the epoxide opening method (46% in 4 steps, Scheme 2.9) and the phthalimide approach (72% in 4 steps, Scheme 2.15).



Scheme 2.21 Synthesis of diazetidine **212** using hydrazine **281**.

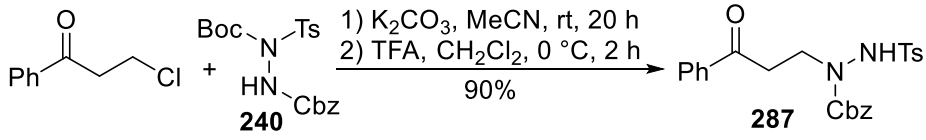
2.6 Synthesis of C3-Substituted Pyrazolidines

Having demonstrated that our strategy employing an ATH reaction was suitable for the synthesis of aryl substituted diazetidines, we next explored whether the synthesis of larger ring sizes would be possible using the same general method. For pyrazolidines we planned to use a hydrazine with just two protecting groups. We thought this would be sufficient for the cyclisation reaction to produce the desired five-membered ring, as it should be favoured even with a carbamate protected terminal nitrogen – unlike when oxadiazine **235** was observed from the cyclisation of precursor **234** (Scheme 2.14). Three different protected hydrazines were reacted with 3-chloropropiophenone to give keto-hydrazines **284**-**286** in good to excellent yields and with excellent regiocontrol (Scheme 2.22). This allowed us to determine how tolerant the subsequent steps were to different protecting groups and allow us to test multiple deprotection and functionalisation strategies on the protected cyclic hydrazines.



Scheme 2.22 Synthesis of keto hydrazides **284**-**286** with different protecting groups.

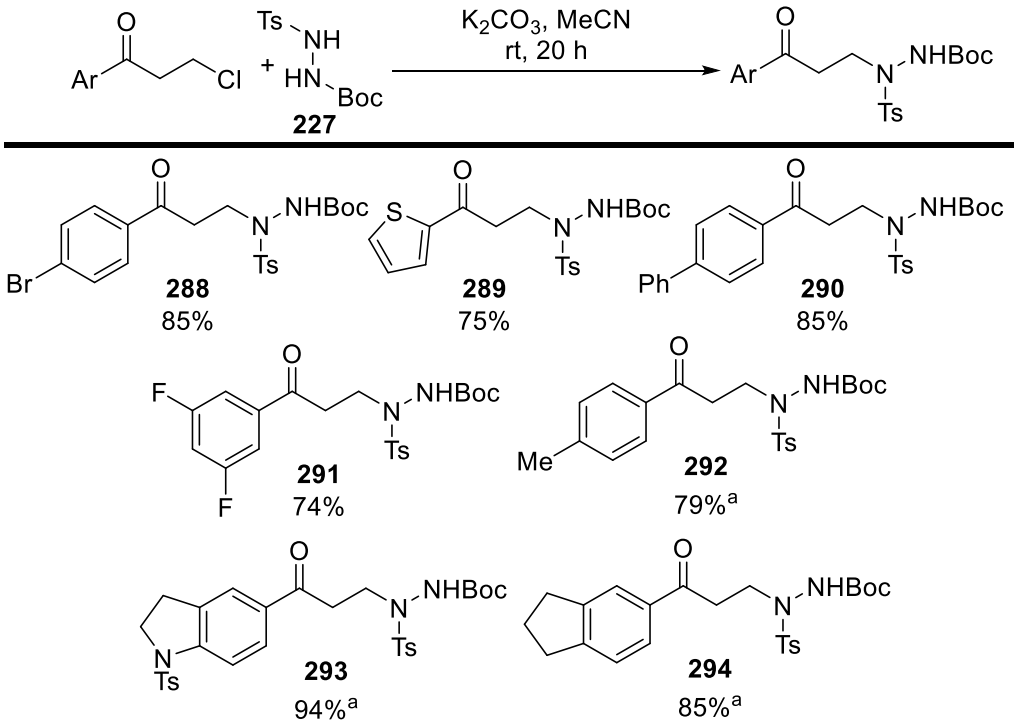
For **287**, in which the carbamate and sulphonamide groups are transposed, triply protected hydrazine **240** was used and **287** was isolated in excellent yield after Boc removal (Scheme 2.23).



Scheme 2.23 Synthesis of keto hydrazine **287** using triply protected hydrazine **240**.

Next, we varied the aryl group to further develop the scope of the reaction, which proved to be possible in good to excellent yields (Scheme 2.24). The Ts

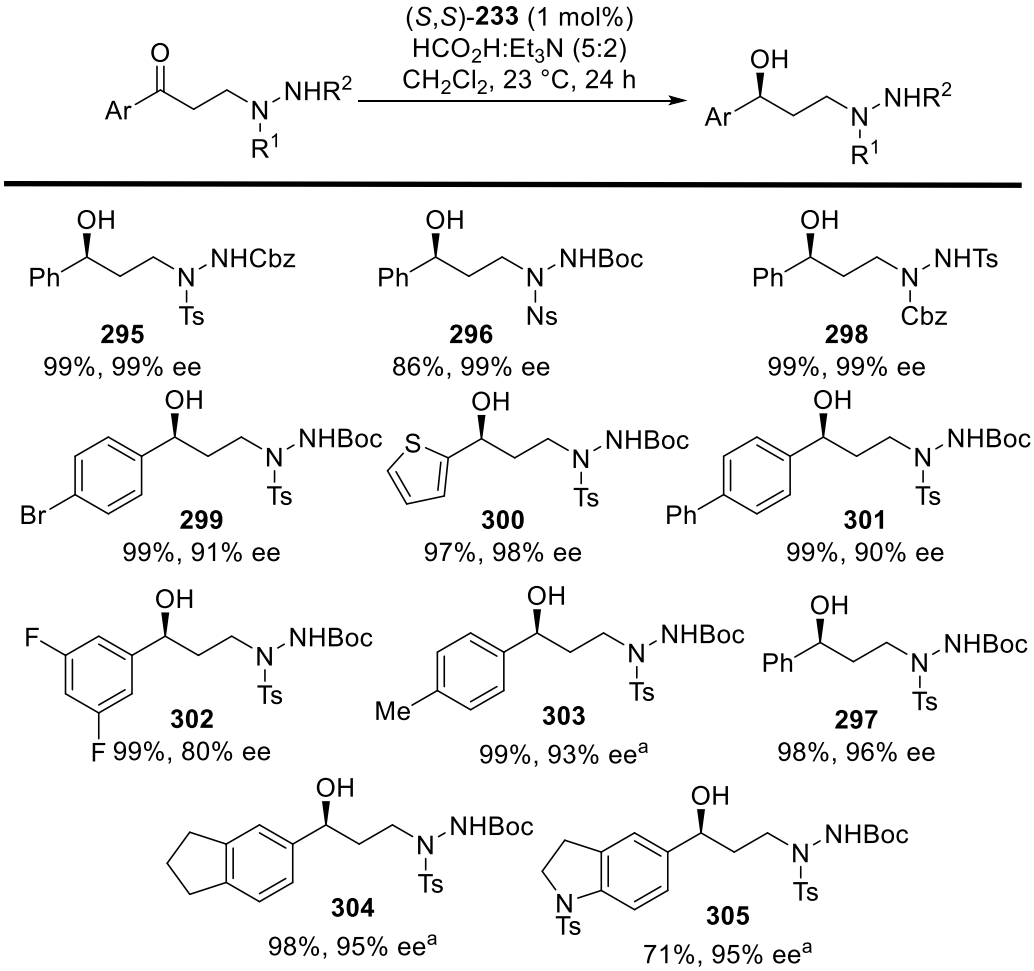
and Boc protected hydrazine **227** was used for all these examples as it gave the best yields for the phenyl derivative (Scheme 2.22, **286**). The aryl chlorides were either commercially available or were synthesised using known procedures (see experimental section for details). Keto hydrazines **288**-**294** were all obtained in good to excellent yields.



Scheme 2.24 Synthesis of keto hydrazides **288**-**294.** [a]Synthesised by Dr Stefan Roeser.

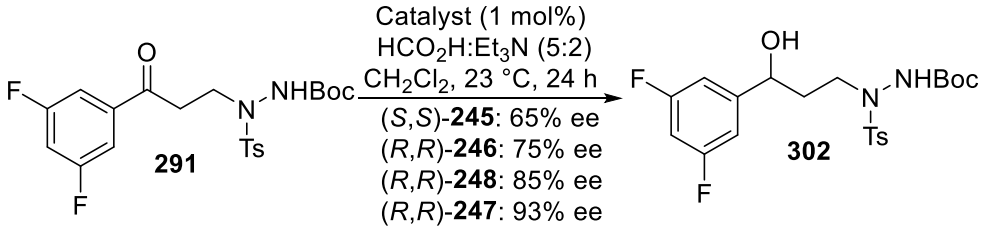
These eleven substrates were then subjected to the optimised ATH conditions and almost all of them transformed to the corresponding alcohols in excellent yields and with high ee (Scheme 2.25). The only exceptions were **305** and **296**, which gave lower yields of 71% and 86% respectively, but with high ee. Conversely **302** was obtained in an excellent yield, but in lower ee.[iv]

[iv] In order to determine ee, two different methods were used. Either the opposite enantiomer of each compound was synthesised using the opposite catalyst enantiomer ie (*R*,*R*)-**233** instead of (*S*,*S*)-**233**. Alternatively, the substrate was reduced using sodium borohydride in methanol to generate an authentic racemic sample for comparison using chiral HPLC. See experimental section for details.



Scheme 2.25 ATH scope for the pyrazolidine precursors. [a]Synthesised by Dr Stefan Roesner.

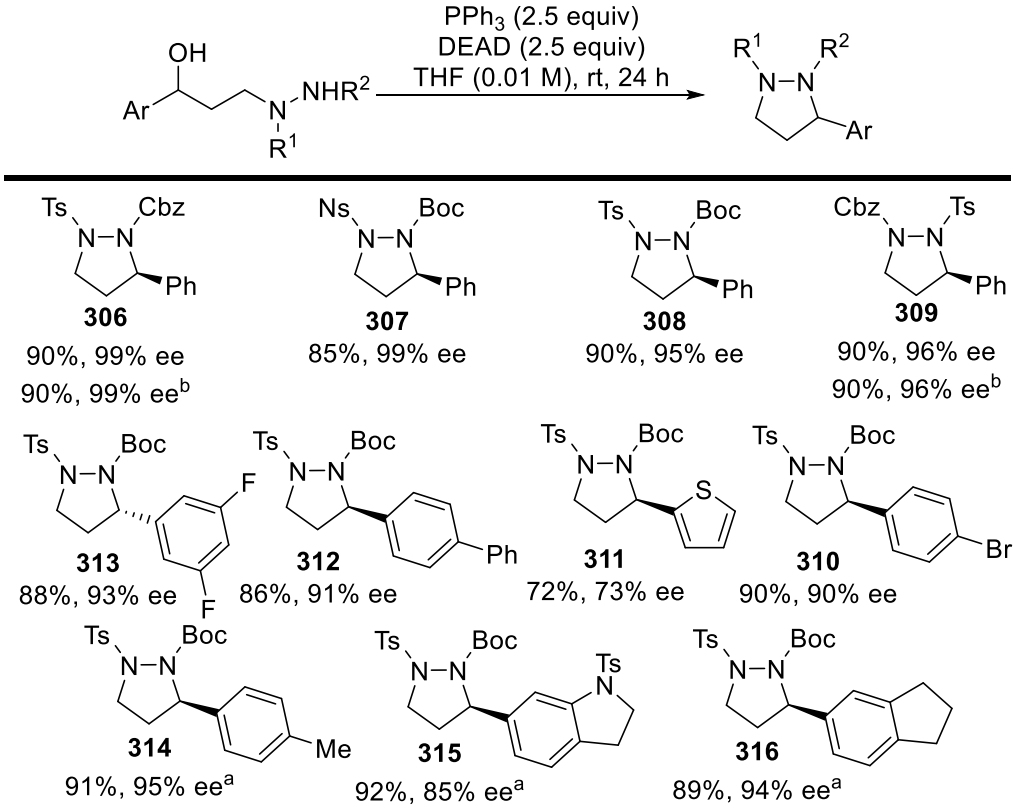
In order to improve the enantioselectivity of the synthesis of **302** several tethered catalysts were screened (Scheme 2.26). The best ee of 93% was achieved with (*R*,*R*)-**247**, which had proven to be similarly effective for the *ortho*-substituted diazetidine precursors **261** and **266**.



Scheme 2.26 Optimisation of the ATH of **291**.

The cyclisation of these alcohols was expected to be less challenging than it was for the diazetidines, as the formation of 5-membered rings is significantly

more kinetically favoured than for 4-membered rings. This proved to be the case, yields were generally excellent for the eleven examples synthesised (Scheme 2.27). Even at higher concentrations of 0.1 M for **306** and **309** the yields were unchanged, which makes the process more practical, especially on larger scales. As expected thiophene example **311** was prone to racemisation, as previously observed for diazetidine **272**, with 73% ee and 62% ee respectively from alcohols **300** (98% ee) and **262** (90% ee).[v]

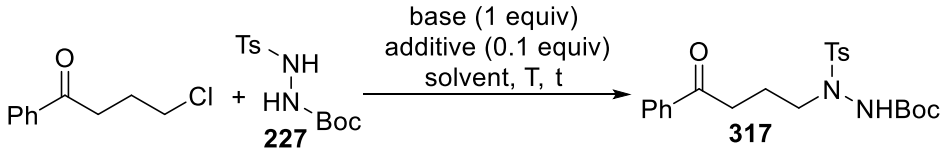


Scheme 2.27 Synthesis of chiral pyrazolidines **306**-**316** using the Mitsunobu reaction. [a]Synthesised by Dr Stefan Roesner. [b]Reaction run in 0.1 M THF

[v] The ee was determined either by synthesising both enantiomers and mixing or by synthesising the racemate and using this as a standard for chiral HPLC. See experimental section for further details.

2.7 Synthesis of C3-Substituted Hexahydropyridazines and Diazepines

Having synthesised the 4- and 5-membered chiral heterocycles we next explored the synthesis of 6-membered hydrazines (hexahydropyridazines), 7-membered hydrazines (diazepines) and 8-membered hydrazines (diazocanes). We first attempted to repeat the S_N2 reaction with 4-chloro-1-phenylbutan-1-one and **227**, which had worked well to synthesise keto-hydrazines with shorter linkers. However, this proved difficult with our standard conditions only yielding starting material (Table 2.4, entry 1). Attempts to use more forcing reaction conditions were also unsuccessful (entries 2-6), additives like TBAI also had little effect, while heating to higher temperatures generally caused decomposition. Using NaH as the base instead of K_2CO_3 gave very slow conversion, however, the reaction was not fast enough to be synthetically viable.

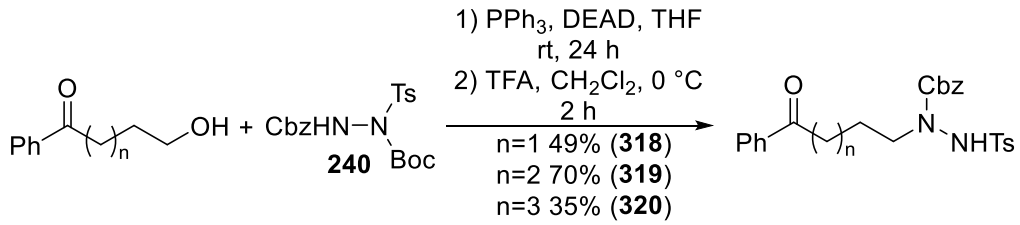


Entry	Base	Solvent	Additive	T	t	Result[a]
1	K_2CO_3	MeCN	None	rt (48 h) to 40 °C (24 h)		NR
2	K_2CO_3	MeCN	TBAI	rt (24 h) to reflux (24 h)		NR (rt) CM (reflux)
3	Cs_2CO_3	MeCN	TBAI	rt (24 h) to reflux (24 h)		NR (rt) CM (reflux)
4	Cs_2CO_3	DMF	TBAI	rt	24 h	Trace **317**
5	NaH	DMF	TBAI	rt	24 h	Trace **317**

Table 2.4 Attempted formation of ketone **317**. [a]By NMR.

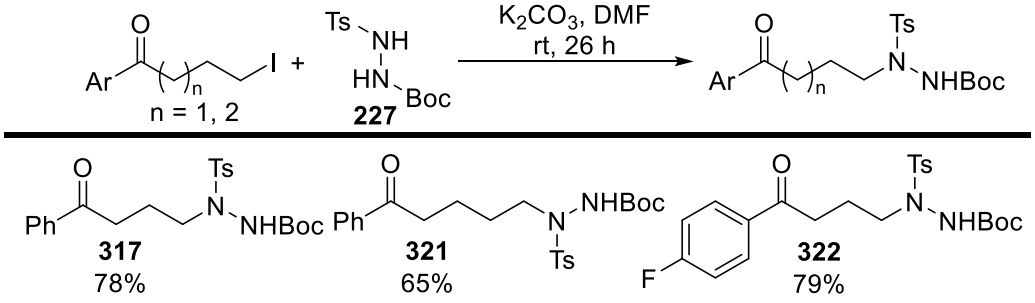
At this point we decided to explore alternative strategies for the synthesis of the desired keto-hydrazides. We were able to synthesise 4-hydroxy-1-phenylbutan-1-one, using a method developed by Sakai *et al.*[97] This alcohol was then reacted with **240** using a Mitsunobu reaction, with subsequent Boc deprotection yielding keto hydrazide **318** in a 49% yield over 2 steps (Scheme

2.28). This process was also effective with 5-hydroxy-1-phenyl-pentan-1-one[98] and 6-hydroxy-1-phenylhexan-1-one,[99] giving **319** and **320** in 70% and 35% yields respectively.



Scheme 2.28 Synthesis of keto-hydrazides with longer carbon linkers.

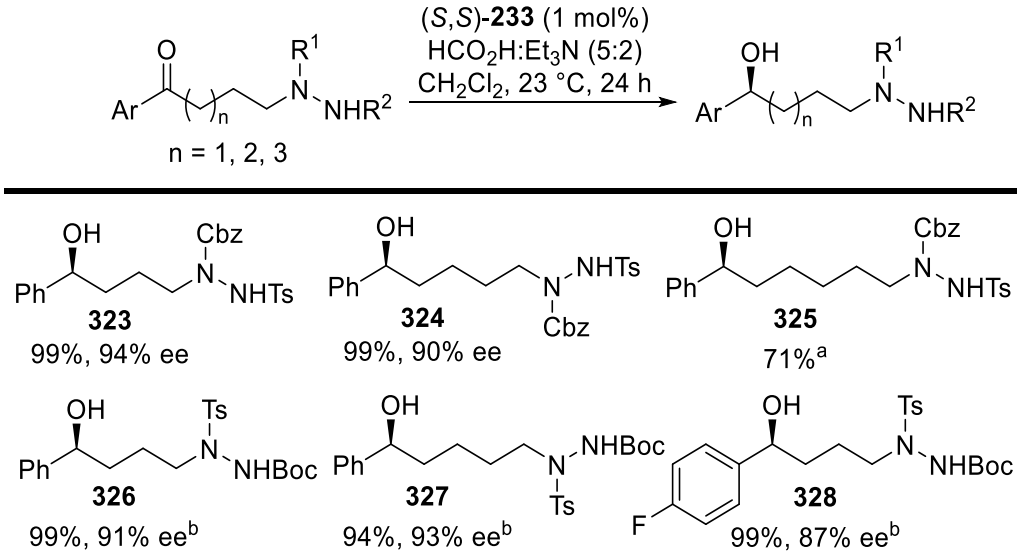
A complementary method for the synthesis of the derivatives was developed by Dr Stefan Roesner, who used alkyl iodides instead of alcohols as starting materials. These iodides were synthesised using known literature procedures[100-102] from the corresponding chlorides. This allowed the keto hydrazine precursors for 6- and 7-membered rings to be synthesised (**317** and **321**), along with 4-fluoro derivative **322** (Scheme 2.29).



Scheme 2.29 Synthesis of keto hydrazides **317**, **321** and **322**. Completed by Dr Stefan Roesner

With these keto hydrazines synthesised we were then able to subject them to the ATH conditions developed previously. All the substrates tested were converted to chiral alcohols in excellent yields and enantioselectivities (Scheme 2.30). The only exception was **325**, the compound with the longest linker, which was isolated in a more modest 71% yield. It was not possible to determine the ee of alcohol **325**, despite multiple attempts using HPLC.[vi]

[vi] In order to determine ee, two different methods were used. Either the opposite enantiomer of each compound was synthesised using the opposite catalyst

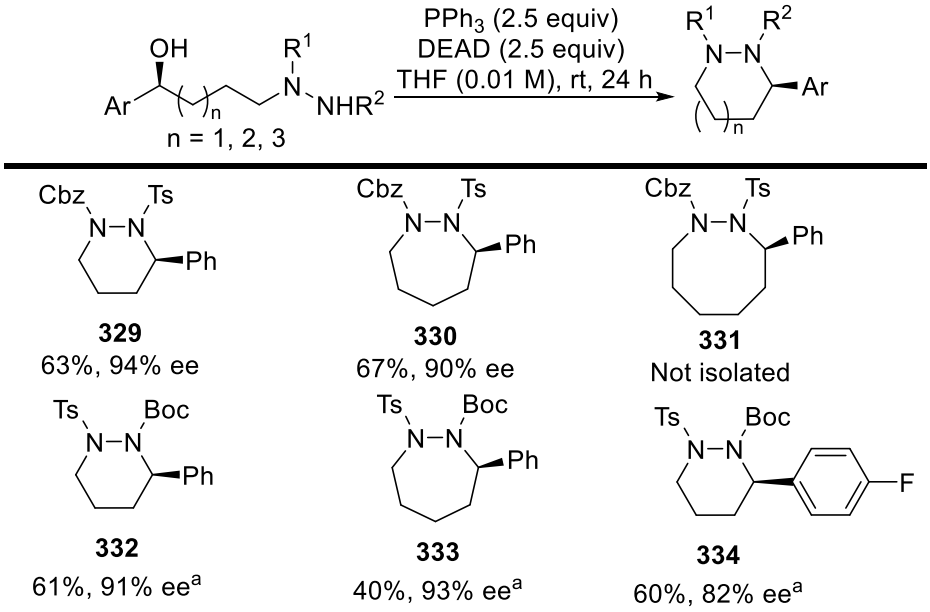


Scheme 2.30 ATH of long chain keto hydrazines. [a]ee could not be determined. [b]Synthesis by Dr Stefan Roesner

The cyclisation of these substrates was expected to be more challenging as the target ring size increased, however we did not observe an especially clear trend (Scheme 2.31). Acceptable yields of the 6- and 7-membered heterocycles **329** and **330** were achieved, however, attempts to synthesise diazocane **331** were not successful. The mass of the desired product was detected by LCMS, however purification by flash chromatography led to a complex mixture that could not confidently be assigned to **331** due to the large number of aliphatic CH_2's in the ^{1}H NMR. No further attempts to isolate this compound were conducted, however higher dilution may have made this possible. The Ts and Boc protected compounds **332-334** were also isolated, in similar yields. As expected, none of the compounds underwent any significant degree of racemisation under the cyclisation, as no strongly electron donating aryl substituents were used.[vii]

enantiomer ie (*R*,*R*)-**233** instead of (*S*,*S*)-**233**. Alternatively, the substrate was reduced using sodium borohydride in methanol to generate an authentic racemic sample for comparison using chiral HPLC. See experimental section for details.

[vii] ee was determined either by synthesising both enantiomers and mixing or by synthesising the racemate and using this as a standard for chiral HPLC. See experimental section for further details.



Scheme 2.31 Mitsunobu cyclisation for larger ring sizes. [a]Synthesis by Dr Stefan Roesner.

2.8 DSC Analysis of Hydrazine Precursors and Cyclic Hydrazines

In this chapter we have explored the synthesis a large number of novel hydrazines, a compound class that has previously been shown to decompose explosively in some cases.[25, 103, 104] Before we proceeded further with larger scale syntheses, we wanted to analyse whether any of the compounds we had made were prone to explosive decomposition. To do this we used differential scanning calorimetry (DSC), which would allow us to identify any potentially problematic exotherms produced by these compounds upon heating. This technique rapidly heats the sample over a wide temperature range and measures any endotherms or exotherms by measuring the change in energy compared with a reference sample. From a safety perspective, it can be used to identify potentially dangerous exotherms, as it measures both their magnitude and their onset temperature. This can be seen with *p*-toluenesulphonylhydrazide (**335**), which has previously been shown to produce a problematic exotherm (Figure 2.3).[105] The exotherm has a relatively low onset temperature of 155 °C and also a large normalized magnitude (932 J g^{-1}), which means the compound is potentially prone to explosive decomposition at an accessible temperature.

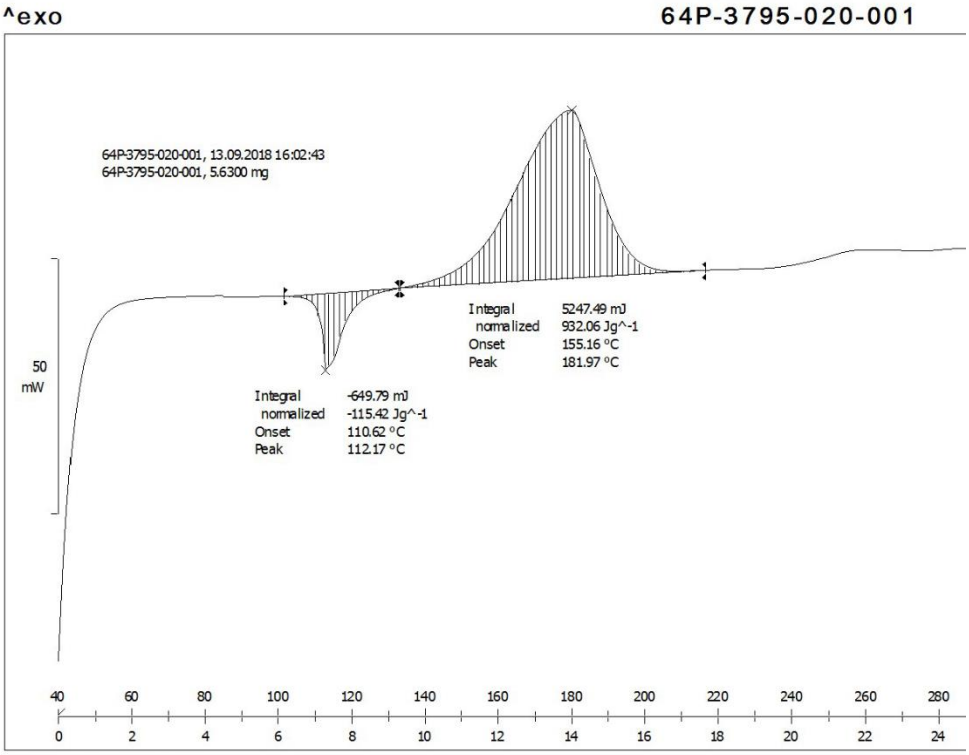


Figure 2.3 DSC of *p*-toluenesulphonylhydrazide **335**.

Further analysis was undertaken on seven hydrazines we had synthesised in order to determine if any of these had significant exotherms associated with them. This was done by comparing the exotherms obtained from DSC analysis against Yoshida's explosion propagation correlation.[106] This plots a normalised heat of decomposition (log Q_{DSC}) against a normalised exotherm onset (log (T_{DSC}-25)), which can be represented graphically on the same graph as the linear Yoshida correlation. Any compounds which appear below the line are unlikely to propagate explosively, although compounds that are near the line are still potential explosion hazards. The plot of our compounds clearly showed that they

are all extremely unlikely to be explosive, giving us greater confidence that scaling up could be done safely (Figure 2.4).

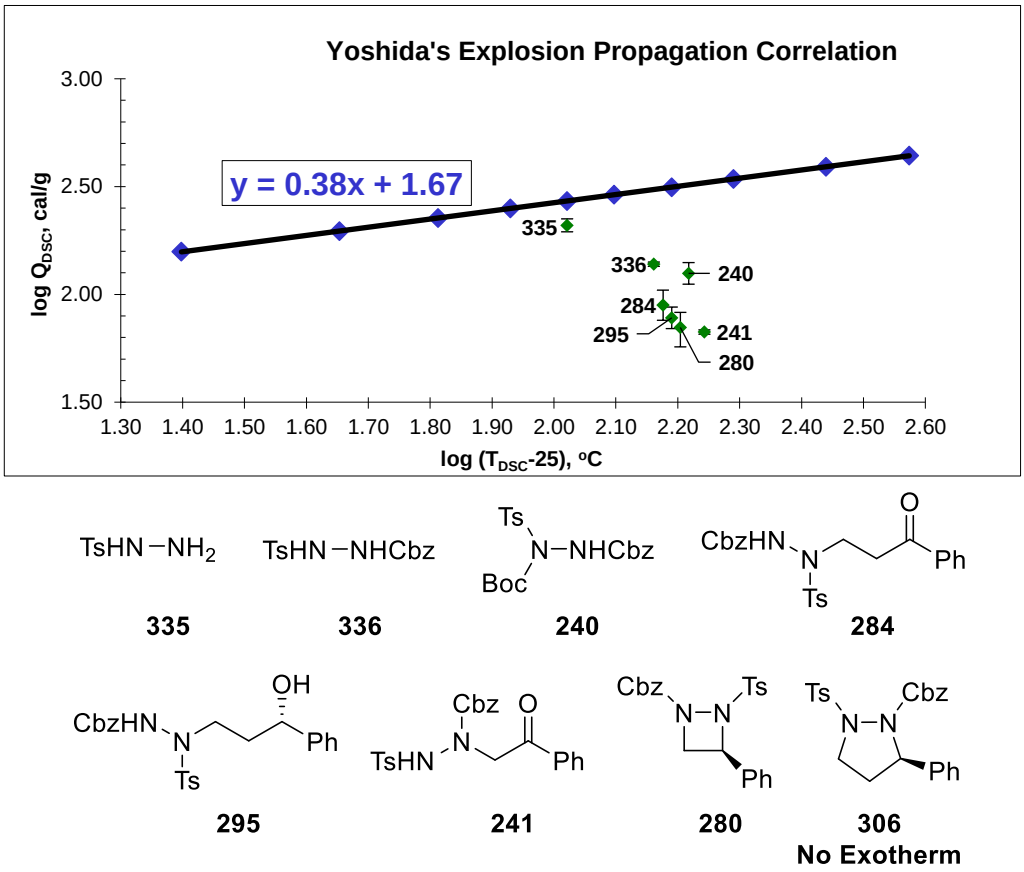


Figure 2.4 DSC analysis of cyclic hydrazines and their synthetic intermediates using Yoshida's explosion propagation correlation.

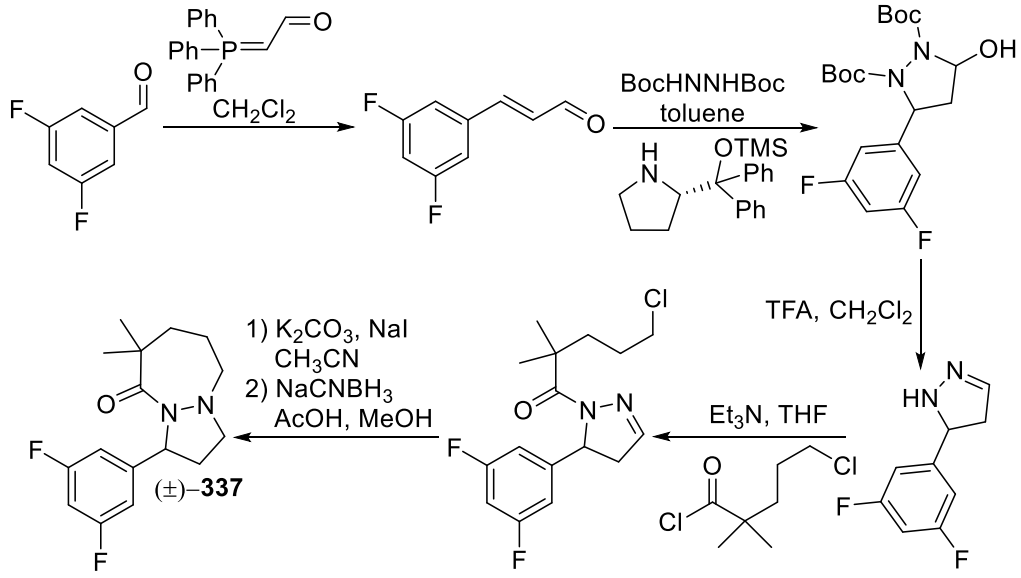
Having shown that these compounds did not have any potentially problematic exotherms we were able to synthesise **280** and **306** on larger scales (up to 5 g), along with Boc protected derivatives **212** and **308**. While conducting this scale up work we also found that by increasing the reaction time of the ATH to 72 h it was possible reduce the loading of catalyst (*S*,*S*)-**233** to just 0.5 mol%, without any erosion in yield or enantioselectivity.

2.9 Towards the Total Synthesis of RipK1 Inhibitor **337**.

As an initial demonstration of the utility of our chiral cyclic hydrazine synthesis in medicinal chemistry we attempted the synthesis of RipK1 inhibitor **337** (Scheme 2.32), which had been shown to be a micromolar inhibitor of the RipK1 enzyme.[107] This receptor has been targeted for a range of human

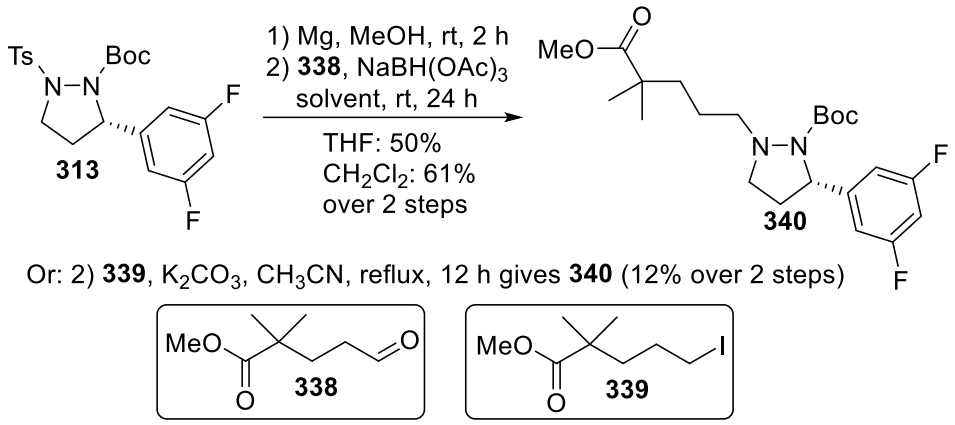
degenerative and inflammatory diseases, including Alzheimer's disease, Parkinson's disease and ALS (Amyotrophic Lateral Sclerosis).

This bicyclic system contains an aryl substituted pyrazolidine and was therefore potentially accessible using our ATH strategy. The synthesis reported in patent WO 2018/213634 A1 required six steps to synthesise the racemate (Scheme 2.32), which then had to be resolved into the two enantiomers using preparatory chiral HPLC. The relative activity of the two enantiomers was not reported, which we would be able to assess by making both enantiomers and determining which was biologically active.



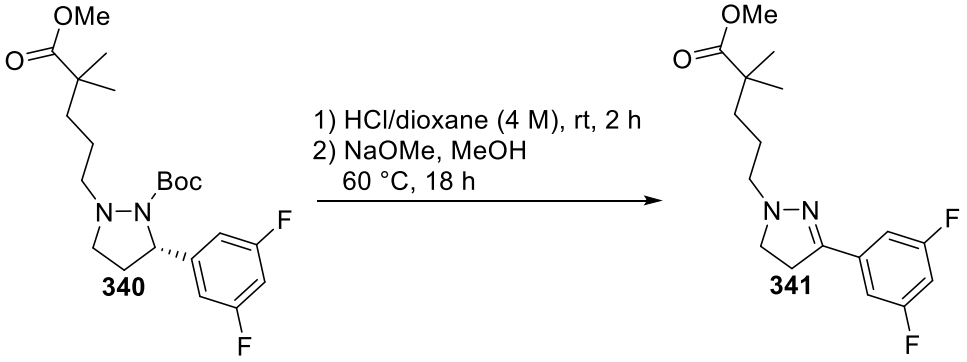
Scheme 2.32 Reported synthesis of RipK1 inhibitor **337**.[107]

We synthesised orthogonally protected precursor **313** in 3 steps with 93% ee using the methodology previously outlined in this chapter. Next, we sought to build the 7-membered ring using an iterative deprotection and functionalisation strategy. We were then able to selectively remove the tosyl group and introduce the carbon chain through reductive amination using aldehyde **338** (synthesised in 2 steps[108, 109]). We synthesised ester **340** in 51% yield, switching from THF to DCM improved the yield to 61% over the two steps (Scheme 2.33). Attempts to use iodide **339**[110] in the formation of **340** was successful but significantly lower yielding (12% over 2 steps).



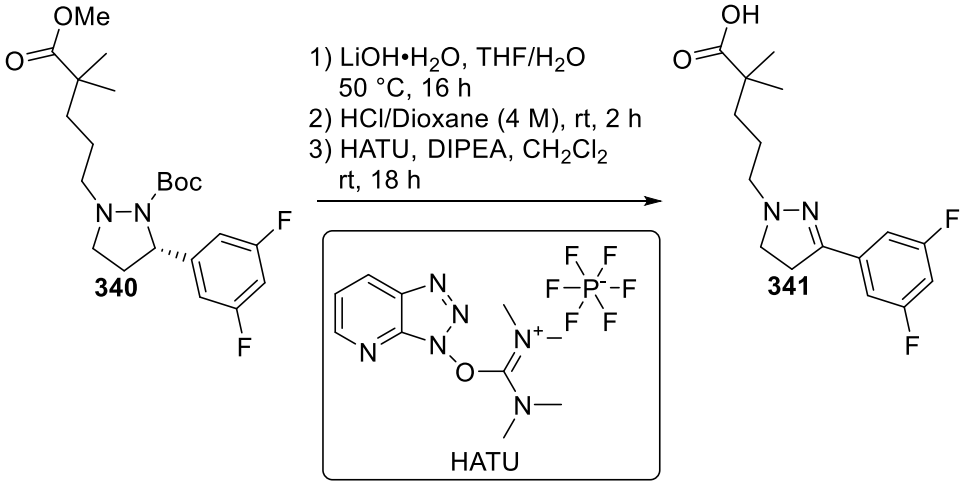
Scheme 2.33 Synthesis of cyclisation precursor **340**.

Removal of the Boc group with hydrochloric acid in 1,4-dioxane to form the HCl salt was successful (Scheme 2.34). However subsequent attempts to cyclise to **337** failed, which was likely due to the formation of imine **341**, although this was not isolated and characterised. This type of oxidation product was subsequently observed in other pyrazolidine examples (Scheme 3.1). Both the mass spec and the crude NMR strongly suggested it was the major product.



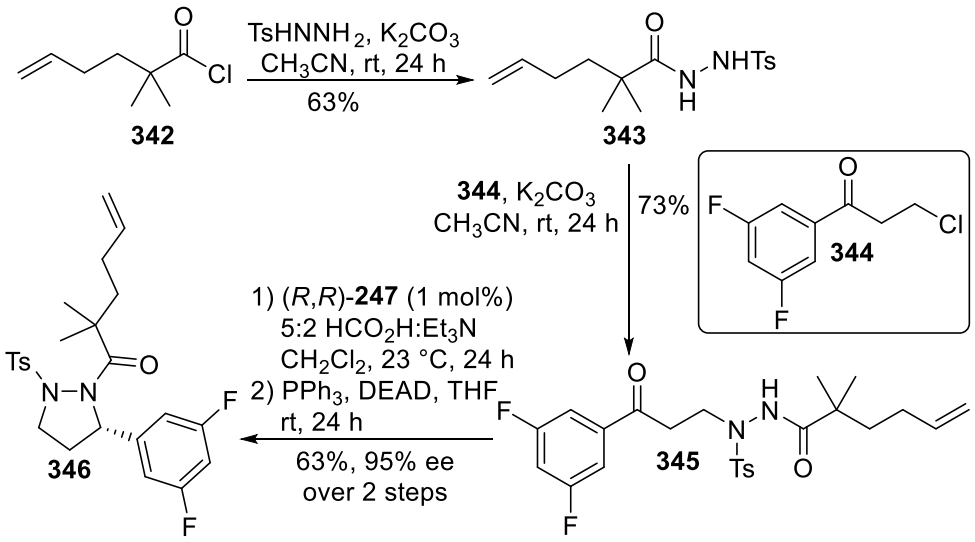
Scheme 2.34 Attempted cyclisation of **340** which gave imine **341**.

Deprotection of the methyl ester to give the corresponding carboxylic acid prior to Boc removal was effective, however attempts to use this substrate for a peptide coupling with HATU again led to imine **341**, with lactam **337** not observed (Scheme 2.35).



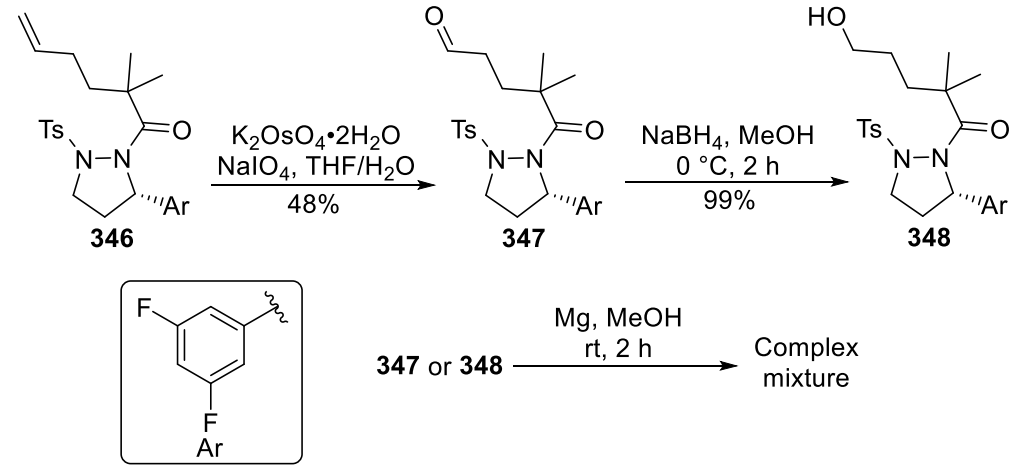
Scheme 2.35 Attempted cyclisation of using a HATU which gave imine **341**.

As this strategy was ineffective, we attempted to alter the final steps by synthesising hydrazine **343** instead, which would not require deprotection of the more hindered nitrogen (Scheme 2.36). Hydrazine **343** was synthesised from acid chloride **342**[111] and *p*-toluenesulphonylhydrazine, and this was then converted to ketone **345** by coupling it with chloride **344**. ATH was completed using catalyst (*R*,*R*)-**247** as this had been the most effective for 3,5-difluoro compound **313**, and for this example it delivered an excellent 98% ee. Subsequent cyclisation using the Mitsunobu reaction gave hydrazine **346** with a slightly reduced ee of 95%.



Scheme 2.36 Synthesis of **346** as a precursor to RipK1 inhibitor **337**.

Next, we converted the alkene of **346** to an aldehyde, which gave **347** in moderate yield (Scheme 2.37). Attempts to treat this aldehyde with magnesium in methanol to remove the tosyl group were not successful, and instead yielded a complex mixture. Subsequently we converted aldehyde **347** to the corresponding alcohol **348**, however this also yielded a complex mixture upon attempts to remove the tosyl group.



Scheme 2.37 Attempted synthesis of Rip K1 inhibitor **337** from hydrazine **346**.

Further work to complete this synthesis is currently ongoing in the group, however, target **337** has not yet been synthesised.

2.10 Conclusions

We have developed a general, enantioselective, high yielding 3-step synthesis of aryl substituted cyclic hydrazides. Twenty-eight different examples were synthesised, across four different ring sizes (4- to 7-membered), with good variation in the aryl groups and protecting groups (both sulphonamides and carbamates) tolerated by this synthetic methodology. This method can also be used to make either enantiomer of each cyclic hydrazide with excellent selectivity simply by switching to the opposite enantiomer of the ATH catalyst.

The synthesis of the keto hydrazides was achieved by utilising simple, reliable S_N2 chemistry. Compounds with two aliphatic carbons or less between the electrophilic halogen and the ketone reacted with the protected hydrazides regardless of which leaving group was used, with even less reactive chlorides

proving effective in the synthesis. The regioselectivity in the S_N2 reaction was also excellent, with the sulphonamide protected nitrogen of the hydrazine reacting preferentially over the carbamate nitrogen in all cases and without the minor regioisomer being observed. In order to reverse this regioselectivity it was necessary to use hydrazines with three protecting groups (**240** and **281**) or phthalimide protected hydrazine **236**. For compounds with longer linkers some optimisation was required due to their lower reactivity, however switching to more reactive iodides and changing the solvent to DMF was sufficient to achieve good yields (Scheme 2.29). Alcohols were also shown to be reactive under Mitsunobu conditions, although this method proved to be less practical as it required more steps and led to lower yields (Scheme 2.28).

The ATH reaction proved to be extremely robust and converted the aryl ketones to the chiral alcohols, in most cases in excellent yields. The measured enantiomeric excesses were almost exclusively >90%, at low catalyst loadings of only 1 mol% of (*S*,*S*)-**233** in the majority of cases. Better results were obtained using catalyst (*R*,*R*)-**247** in three examples, two with *ortho* substituents (**261** and **266**) and difluoroaryl derivative **302**.

The cyclisation using the Mitsunobu reaction proved to be the most challenging step, particularly for the smallest and largest ring sizes. Synthesis of 1,2-diazetidines was the most challenging, with sulphonamides required on the terminal nitrogen in order to cyclise to the required 4-membered ring. Even at high dilution, yields proved to be variable. 5-Membered rings were generally synthesised in excellent yields, while 6- and 7-membered rings also worked well. The most significant drawback of the cyclisation was the epimerisation that occurred for substrates bearing strongly electron donating aryl groups like thiophenes, where significant erosion of ee was observed.

We also developed a complementary method to synthesise orthogonally protected chiral diazetidines. We were able to ring open readily available chiral epoxides using hydrazine monohydrate, then subsequently install the Boc and Ts protecting groups sequentially in good yields, which generates alcohols complementary to those synthesised using the ATH method. This method

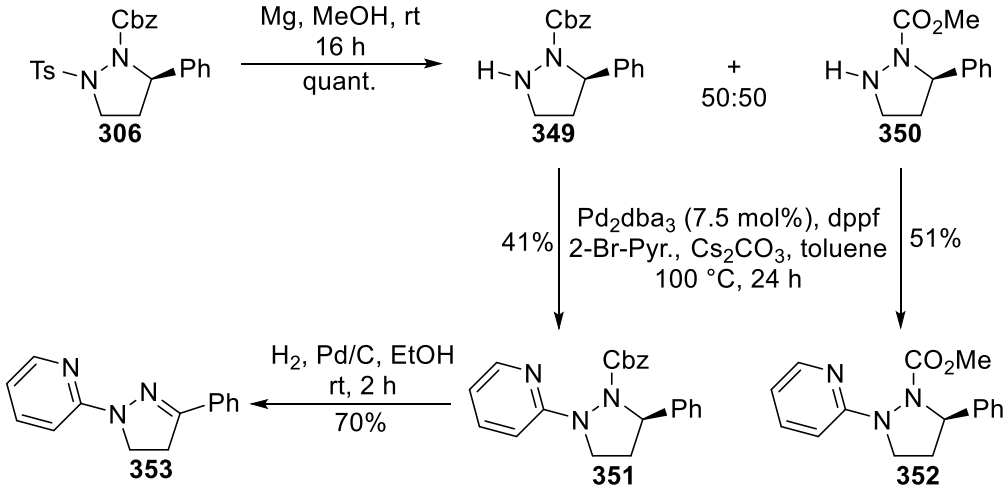
provides an alternative approach to synthesising aryl substituted diazetidines and is also tolerant of alkyl groups in this position (e.g. CH_2OPh).

Finally good progress towards the synthesis of RipK1 inhibitor **337** has been achieved, although completion of the synthesis has thus far proven elusive. Synthesis from hydrazine **313** was not successful, with the final cyclisation step generating undesired imine **341**. The alternative strategy obivated the need for this final cyclisation, however the final detosylation proved equally problematic and **337** was again not obtained.

Chapter 3 Towards Libraries of Cyclic Hydrazines

3.1 Deprotection and Cross-Coupling of Pyrazolidines

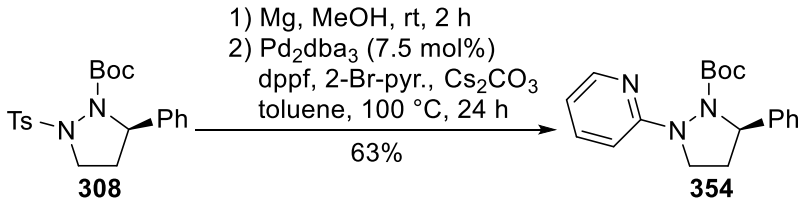
Having synthesised a set of more than twenty orthogonally protected cyclic hydrazines we next sought to deprotect and functionalise them by adding fragments to each nitrogen. Our initial studies used pyrazolidines, as they had been synthesised in high overall yields in just three steps on up to 5 g scale. We had prepared examples with different pairs of protecting groups to clarify which combinations were most suitable. Studies began with cyclic hydrazine **306** with Ts and Cbz protecting groups. Initially we attempted to selectively remove the Ts group, using conditions that had previously been applied to similar substrates,[39] however we observed a 1:1 mixture of **349** alongside methyl carbamate **350** resulting from transesterification of the benzyl group (Scheme 3.1). These were separated using preparative HPLC and both subsequently underwent Buchwald-Hartwig cross couplings using literature conditions optimised for similar substrates,[112] to give **351** and **352** respectively. Despite employing reducing conditions to remove the Cbz group of **351** *via* hydrogenation, oxidation to imine **353** was observed, which removed the stereocentre.



Scheme 3.1 Deprotection and functionalisation of pyrazolidine **306**.

Instead of attempting to further optimise this sequence, we instead switched to pyrazolidine **308** protected by Ts and Boc groups. We expected the Boc group

to be more stable during the Ts group removal due to the increased size of the *tert*-butyl group. This proved to be the case, and the amine was readily formed after only two hours (Scheme 3.2). Purification was challenging as the substrate was not stable to chromatography, however when used directly in the cross coupling[112] without purification we were able to isolate pyridine **354** in an encouraging 63% yield.



Scheme 3.2 Deprotection and functionalisation of pyrazolidine **308**.

Next, we sought to further optimise the Buchwald-Hartwig coupling. This was done in collaboration with Nessa Carson while on placement at Erl Wood with Eli Lilly and Co. We were able to conduct ninety-six experiments in parallel with amine **355**, using high throughput equipment and in-house software.[113] This allowed us to screen twelve different catalyst/ligand systems, with four different bases and two solvents (toluene and 1,4-dioxane) simultaneously. This screening highlighted several potentially viable sets of reaction conditions (Figure 3.1) and provided valuable information about optimal conditions for the cross coupling of cyclic hydrazines. The size of the pie charts indicates how much of the material analysed by LCMS could be assigned to one of the products in the scheme, with green representing product **354**. Smaller pie charts reveal other unknown impurities are present. From this data we were able to conclude that: toluene is marginally better as a solvent than 1,4-dioxane, sodium *tert*-butoxide is the best base, and Pd-162, Pd-170 and Pd-171 are the best catalyst/ligand combinations (Figure 3.2 for catalyst structures). These catalysts were developed by Johnson Matthey as highly active catalysts stable to air and moisture.[114] They also don't readily form catalytically inactive dinuclear palladium species.

Figure 3.1 96 well screen of conditions for the cross coupling of **355**. Completed in collaboration with Eli Lilly/AMRI.

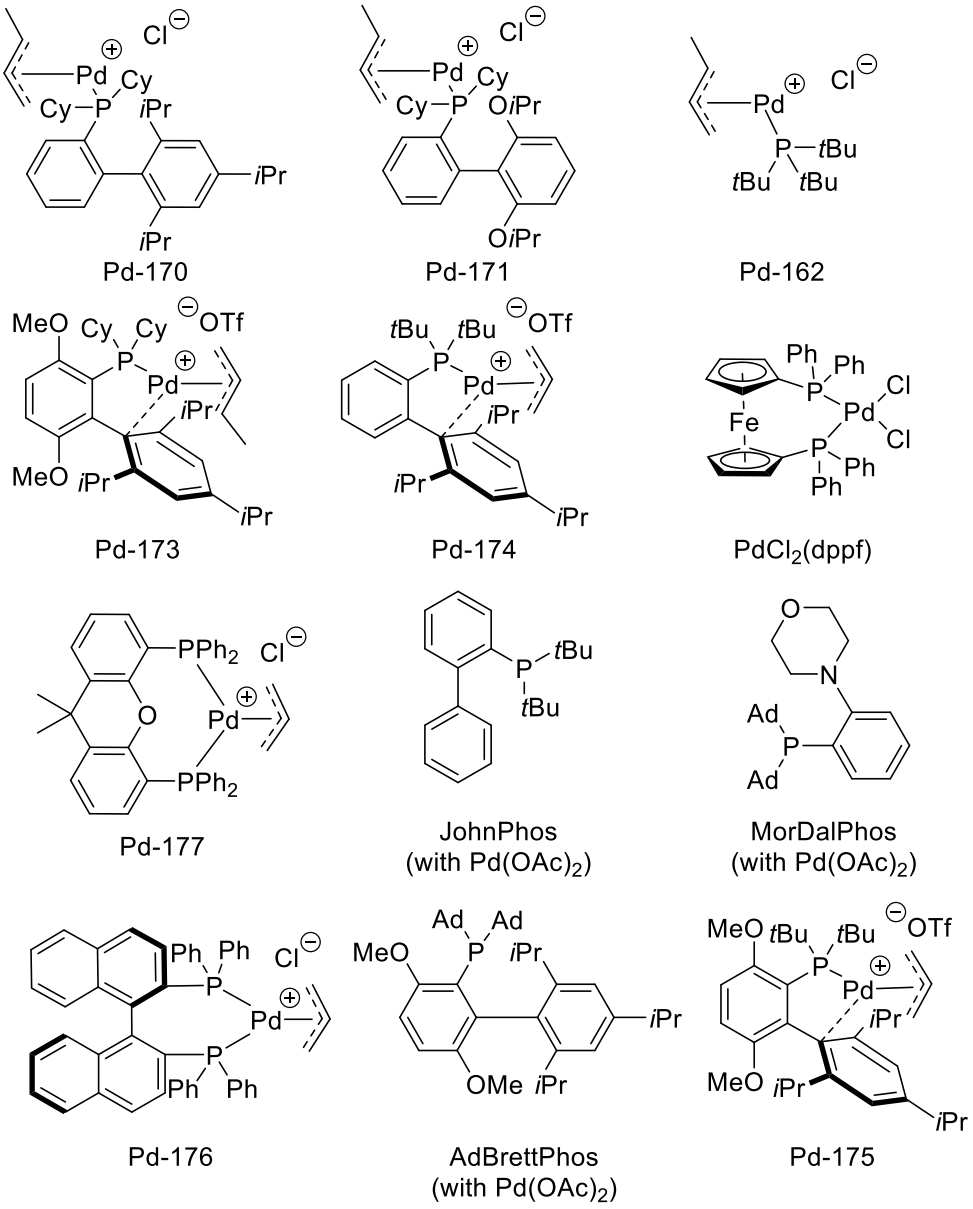
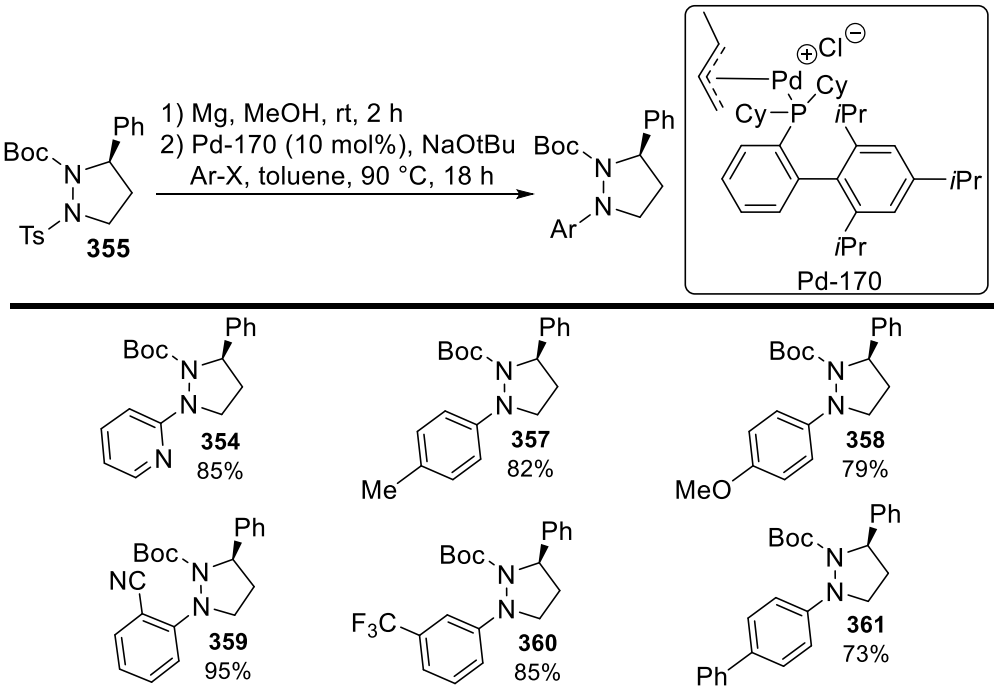


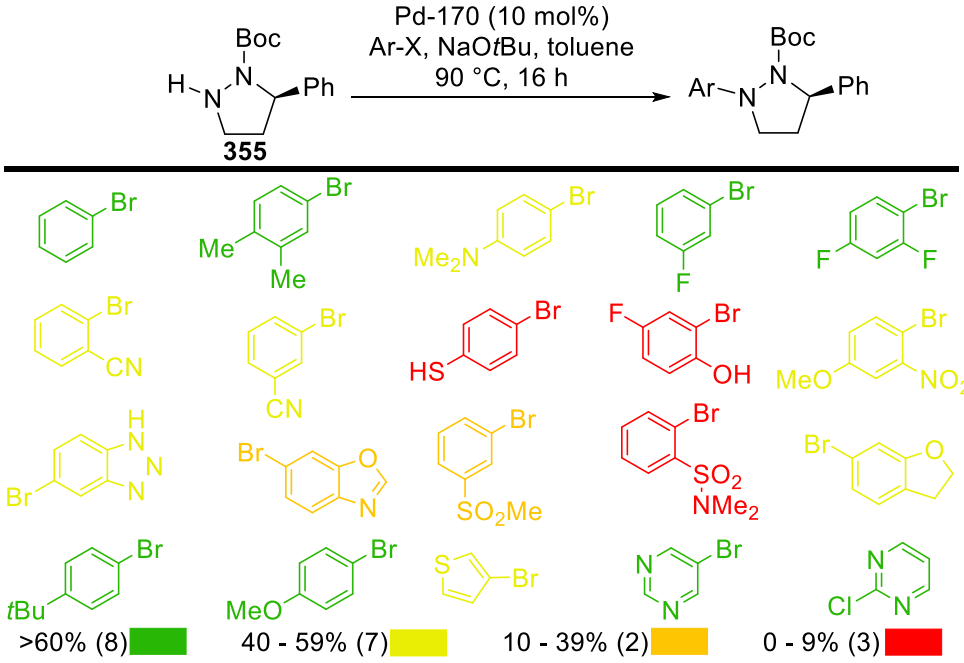
Figure 3.2 Structures of the twelve catalysts/ligands screened.

Repeating the synthesis of **354** from **355** on a 100 mg scale in a round bottom flask using Pd-170 with sodium *tert*-butoxide and toluene, provided **354** in an improved yield of 85%. Next, we explored the scope of this reaction, choosing several aryl halide coupling partners of differing reactivity. These conditions proved to be extremely effective for all substrates studied, giving **357**-**361** in good to excellent yields (Scheme 3.3).



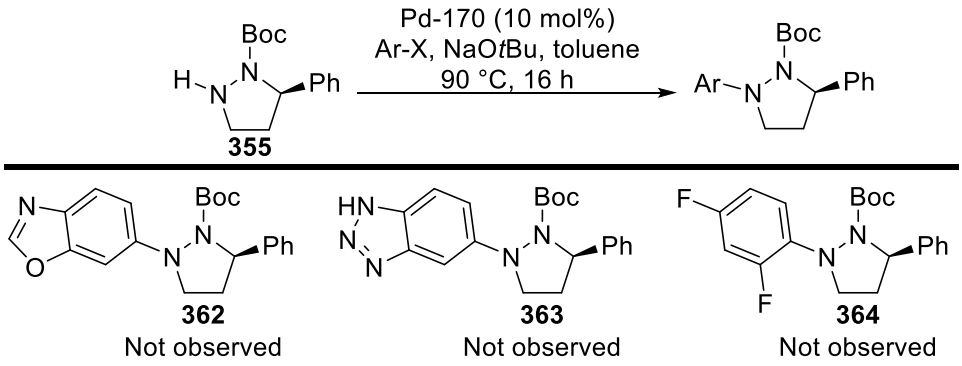
Scheme 3.3 Scope of the Buchwald-Hartwig coupling of **355** using Pd-170.

In collaboration with Nessa Carson another high throughput screen was carried out. This time we subjected twenty different aryl halides to the optimised cross coupling conditions with **355**, which showed most aryl halides (15/20 in >40% conversion) could be used in this coupling (Scheme 3.4).



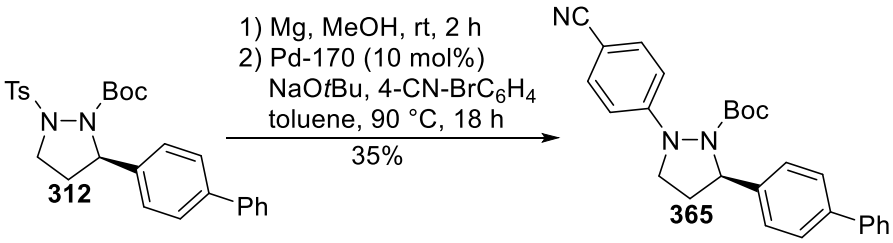
Scheme 3.4 Aryl halide screen using **355** completed with Nessa Carson.

Subsequent analysis however showed that this screen was not an especially reliable predictor of coupling partner suitability. 2-Bromobenzonitrile was identified as a moderately well tolerated halide in the screen (40-59% conversion), however it was in fact an excellent coupling partner (**359** isolated in 95% yield – Scheme 3.3). Additionally, couplings with halides 5-bromo-1*H*-benzo[*d*][1,2,3]triazole, 1-bromo-2,4-difluorobenzene and 6-bromobenzo-[*d*]oxazole were attempted on a 100 mg scale in a round bottom flask, however **362**-**364** were not seen by LCMS or when the crude mixture was analysed by ^{1}H NMR (Scheme 3.5). The reasons for the large discrepancy between the data from the screen and the results of the scale up experiments is not clear. It is possible that the LCMS method used to analyse the high throughput screen was highlighting false positive results for some examples and incorrectly identifying impurities in others. The screening method was not designed to screen the results obtained with different coupling partners and it is clear from this data it is not suitable for this.



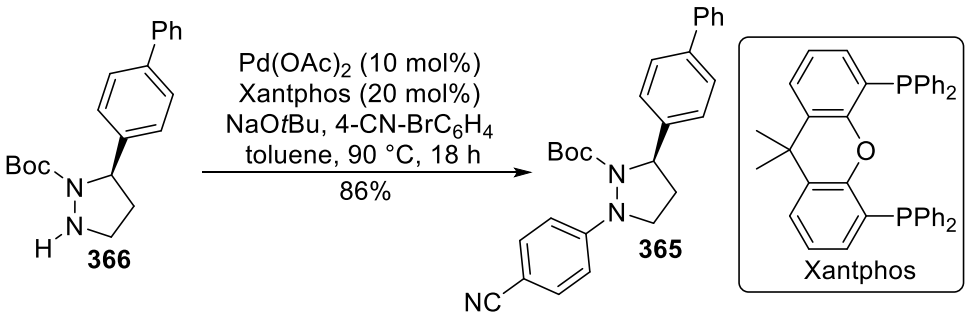
Scheme 3.5 Attempted synthesis of **362**-**364**.

Attempts to expand the scope to pyrazolidines with other aryl groups proved more challenging. Biphenyl substituted pyrazolidine **312** could be deprotected to using magnesium in methanol, however the cross-coupling only gave product **365** in a modest 35% yield under the previously optimised reaction conditions (Scheme 3.6).



Scheme 3.6 Deprotection and coupling of biphenyl substituted pyrazolidine **312**.

Further optimisation was undertaken to identify a better catalyst system for this coupling, as deprotection of **312** to give **366** was essentially quantitative. Solvent and base optimisation was not attempted, toluene and sodium *tert*-butoxide were assumed to be optimal for this coupling based on previous evidence (Figure 3.1). $Pd(OAc)_2$/Xantphos had been identified as an effective catalyst system in cyclic hydrazine cross couplings that we were optimising simultaneously (Scheme 3.24). Using this catalyst also proved effective here, with **365** isolated in 86% yield (Scheme 3.7).

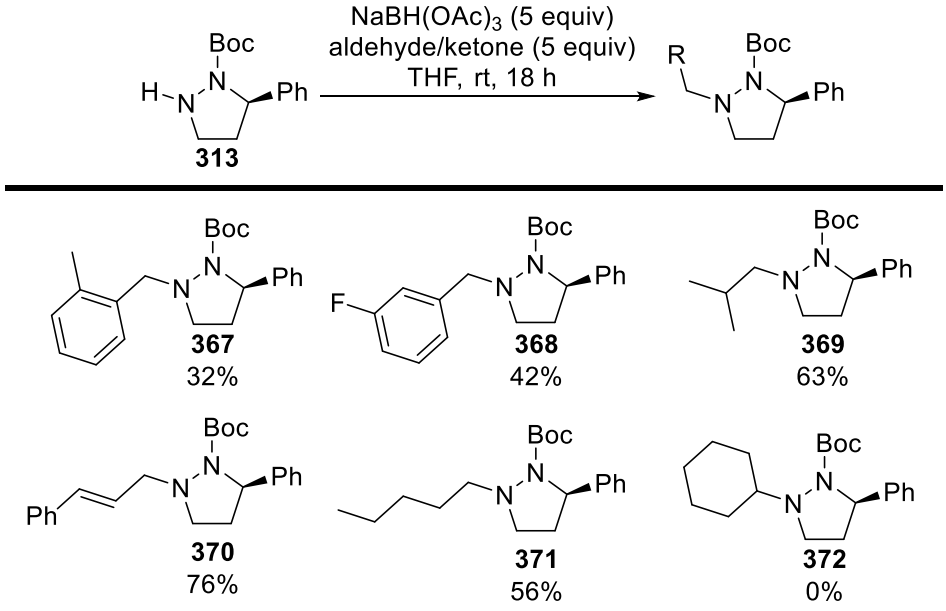


Scheme 3.7 Optimised cross coupling of **366** using $Pd(OAc)_2$ and Xantphos.

3.2 Other Functionalisation Reactions Using Aryl Pyrazolidines

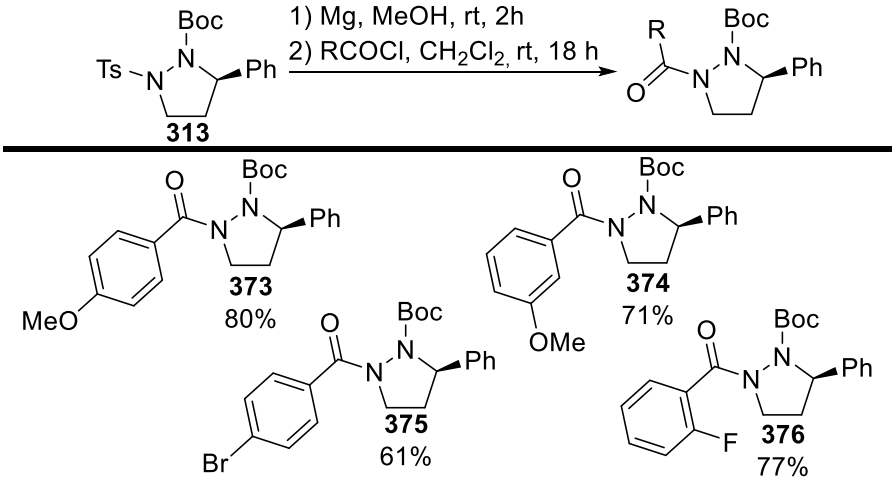
Having optimised the Buchwald-Hartwig coupling of **313** and **366**, we next turned to other widely used nitrogen functionalisation reactions to further expand the product scope. We started with reductive amination and utilising conditions developed by Abdel-Magid *et al.*,[115] we were able to couple amine **313** with a series of aldehydes to give **367**-**371** (Scheme 3.8). Attempts to form **372** by using cyclohexanone was unsuccessful which is likely due to the difficulty in forming the hindered imine. In order to drive the reaction to completion in a synthetically viable timescale it was necessary to use five

equivalents of the aldehyde and sodium triacetoxyborohydride, which meant there was often a significant amount of alcohol by-product from the reduction of the aldehyde in the reaction mixture. Separation using flash chromatography proved challenging but was successful, although some substrates required multiple purifications leading to greater material loss (see experimental section).



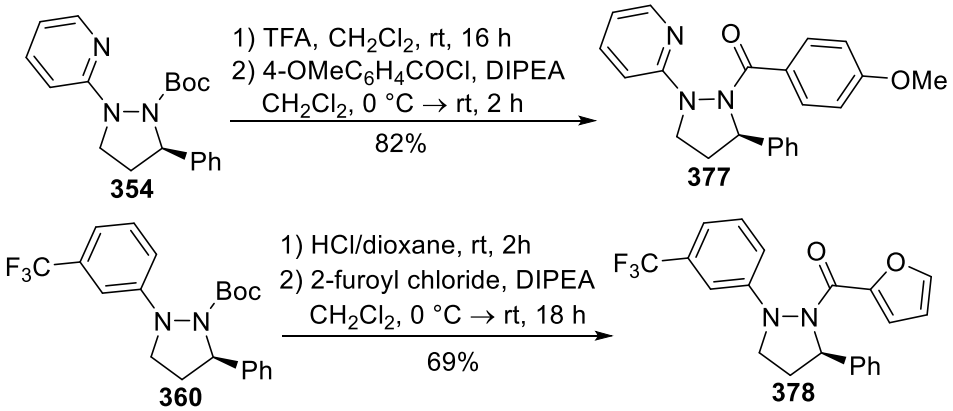
Scheme 3.8 Scope of the reductive amination using **313**.

We next explored the acylation of amine **313**. Four examples were synthesised which showed a variety of aryl groups were tolerated and gave the hydrazines **373**-**376** in good yields (Scheme 3.9).



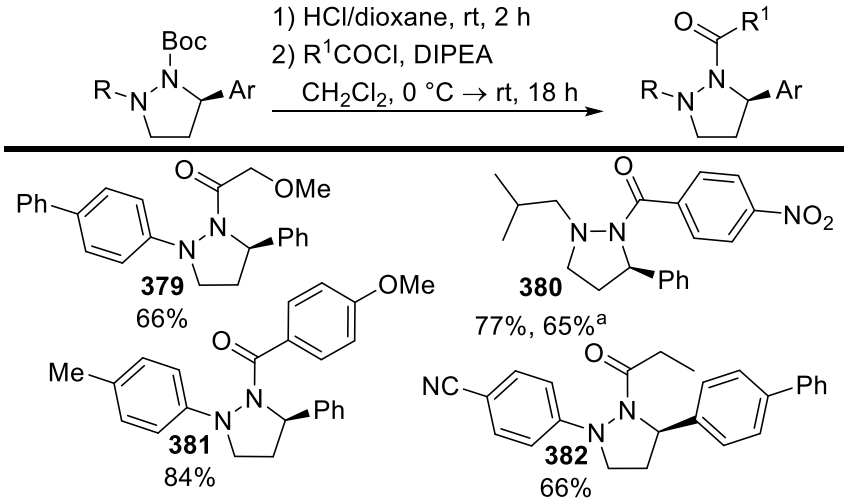
Scheme 3.9 Scope of the acylation reaction using **313**.

Having shown a range of chemistries can be used to functionalise the less hindered nitrogen of pyrazolidine **308**, we next turned to functionalisation at the nitrogen adjacent to the C3 substituent. We knew this would be more difficult as we had already observed that removing the protecting group on this nitrogen left the resulting amine prone to oxidation to the corresponding imine (Scheme 3.1). However, by converting the free amine to its TFA or HCl salt we were able to acylate this nitrogen in good yields, using the TFA salt for **377** and the HCl salt for **378** (Scheme 3.10).



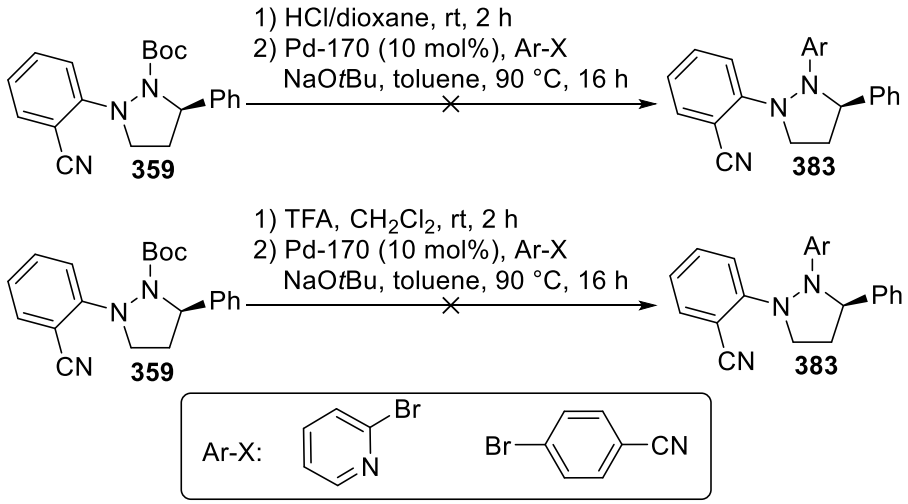
Scheme 3.10 Acylation of the nitrogen atom adjacent to C3.

This transformation was successful for four other examples, with **379**-**382** all synthesised in good yields (Scheme 3.11). The HCl salt was used for these transformations as it was found to give better yields than using TFA for **380**.



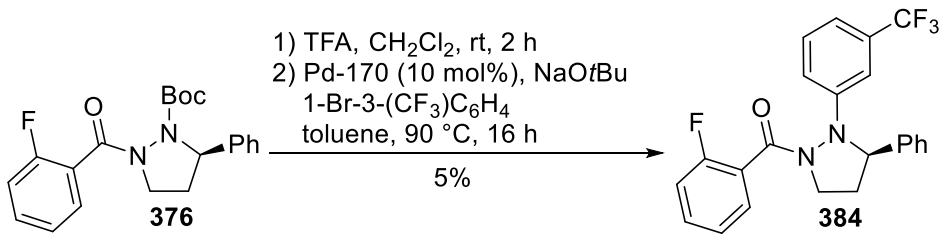
Scheme 3.11 Acylation on the nitrogen atom next to C3. [a]Deprotection with TFA/CH_2Cl_2.

Having found suitable conditions for acylation, we next attempted the Buchwald-Hartwig coupling on this nitrogen atom. This reaction employs a rather hindered nitrogen nucleophile, and there is a competing oxidation side reaction to the undesired imine, so this transformation was expected to require significant optimisation. We speculated that use of the salt of the amine might inhibit this competing process by limiting the concentration of free amine in solution but we expected this to be significantly more challenging as there is only limited literature precedent for cross couplings using ammonium salts.[116] Initial attempts using **359** were unsuccessful, with only trace amounts of **383** detected by LCMS when using our previously optimised Buchwald-Hartwig conditions to attempt to couple both 2-bromopyridine and 4-bromobenzonitrile (Scheme 3.12). Similarly disappointing results were observed using either the HCl or TFA salt of **383**.



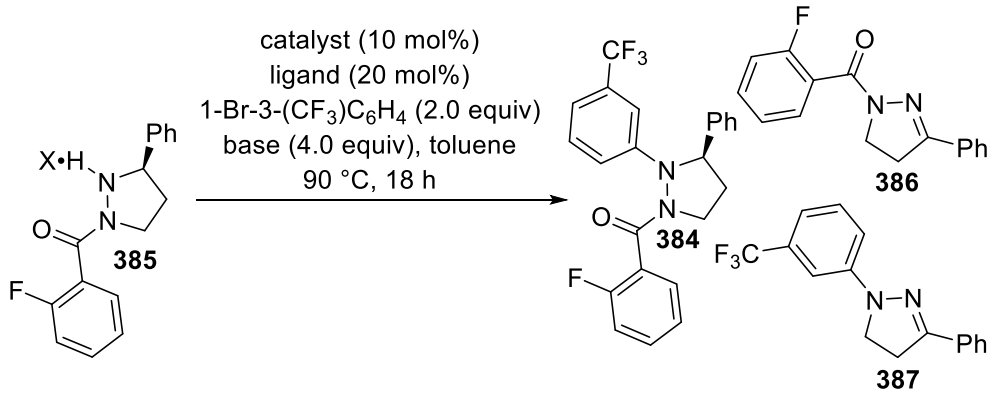
Scheme 3.12 Attempted cross coupling of both the TFA and HCl salts of **359**.

As this approach was not successful, we examined the coupling of pyrazolidine **376** with 3-bromobenzotrifluoride (Scheme 3.13). Although the yield for this transformation was only 5%, it gave us an authentic sample of coupled product **384**. This allowed us to analyse the sample by GCMS and construct a calibration curve (Table 6.3), which meant further screening could be conducted more efficiently and would also allow us to obtain quantitative data.



Scheme 3.13 Synthesis of pyrazolidine **384**.

We conducted a small screen of catalysts, bases and solvents on **385** in order to improve this transformation. As we had observed previously (Figure 3.1), sodium *tert*-butoxide and toluene remained the best base and solvent combination, outperforming potassium carbonate and 1,4-dioxane in all cases (Table 3.1). Palladium acetate and Xantphos was the most effective catalyst system (entries 4, 6 and 7). Finally, we observed that the HCl salt gave better conversion than the corresponding TFA salt (entries 4 and 6). We were able to use GCMS and ^{1}H NMR to assign plausible structures to some of the major by-products formed in the reaction; imine **386** was an unsurprising by-product, however the formation of imine **387** was not expected. Its presence suggests that with certain catalytic systems (entries 1 and 5), the palladium can insert into the amide bond of **386**, followed by cross coupling on the less hindered nitrogen to give **387**. This type of decarbonylative cross coupling of amides with palladium catalysts has previously been reported in the literature for other amides and there are several reviews available on this subject.[117, 118]



Entry	X	Conditions	Conv.[b]	Yield
1	TFA	Pd-170, NaO*t*Bu	23	5
2	TFA	Pd-170, NaO*t*Bu[a]	7	-
3	TFA	Pd-170, K_2CO_3	9	-
4	TFA	$Pd(OAc)_2$, Xantphos, NaO*t*Bu	42	22
5	TFA	$Pd(OAc)_2$, Xphos, NaO*t*Bu	38	-
6	HCl	$Pd(OAc)_2$, Xantphos, NaO*t*Bu	59	40
7	HCl	$Pd(OAc)_2$, Xantphos, NaO*t*Bu[a]	53	-
8	HCl	$Pd(OAc)_2$, Xantphos, K_2CO_3	8	-
9	HCl	$Pd(OAc)_2$, Xantphos, K_2CO_3[a]	0	-

Table 3.1 Optimisation of the coupling of **385**. [a]In dioxane. [b]By GCMS analysis

Although we had significantly improved the isolated yield, it was still only a relatively modest 40% under the optimised conditions. In order to increase the yield beyond this we were again able to collaborate with Nessa Carson and conduct a larger screen of catalysts. As **385**·HCl was difficult to synthesise on a large scale and we had already determined that 1,4-dioxane was inferior to toluene as a solvent for this transformation, we decided to omit it, meaning we screened forty eight reaction conditions. We only made one other change to the screening table, replacing palladium acetate/JohnPhos with Pd-180 (Figure 3.3).

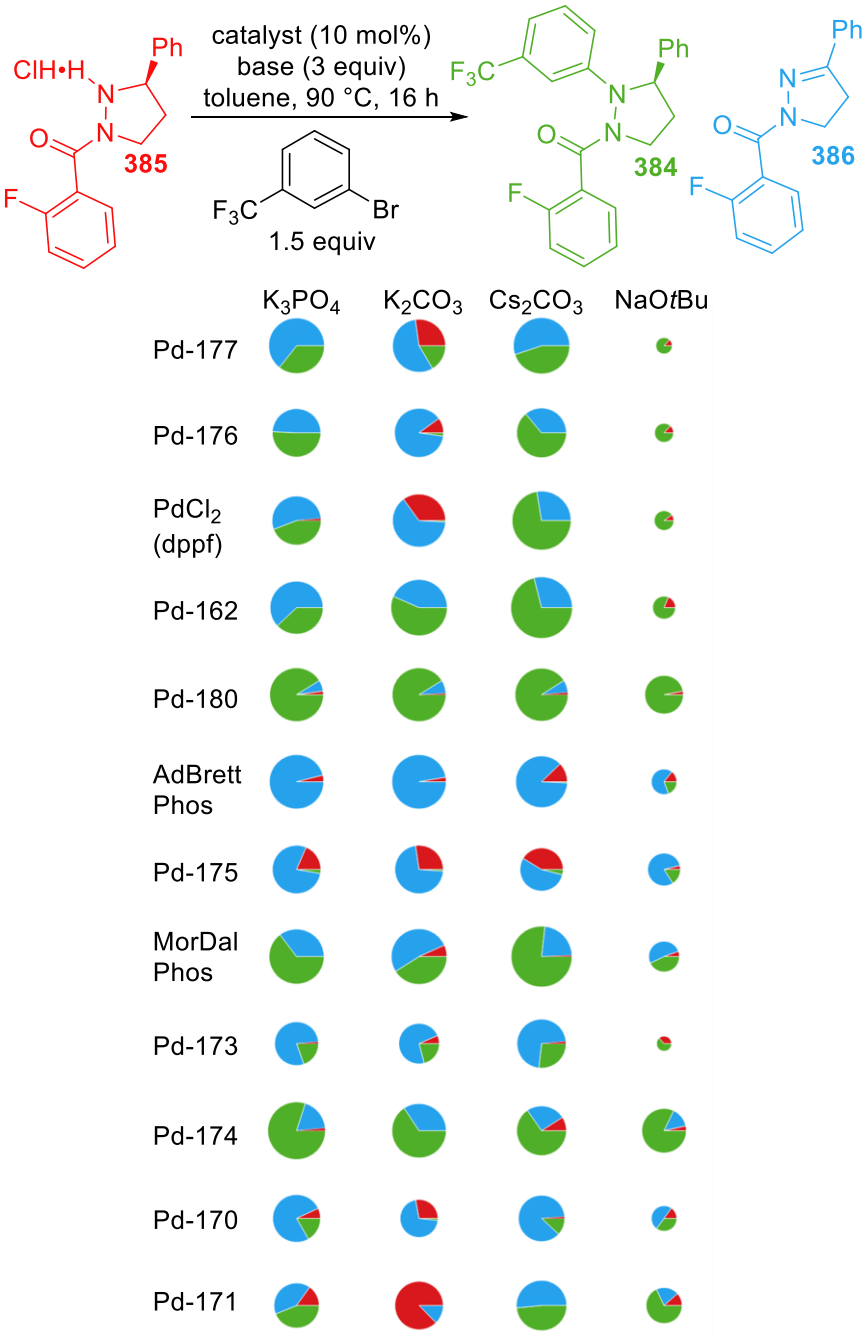
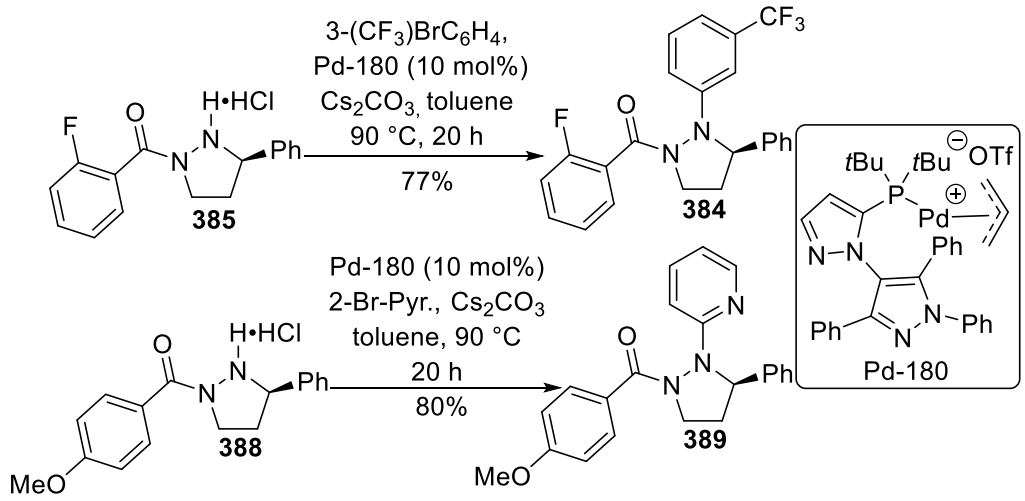


Figure 3.3 Further optimisation of the Buchwald-Hartwig coupling of HCl salt **385**. Completed in collaboration with Eli Lilly/AMRI.

It is clear when comparing Figure 3.1 with Figure 3.3 that **385**·HCl was a more challenging substrate than **355**. The majority of the catalysts screened only gave low conversions, with sodium *tert*-butoxide in particular proving to be an ineffective base for this transformation. Instead caesium carbonate was a more effective, while only a limited number of catalyst systems gave encouraging

results. We selected Pd-180 and caesium carbonate as the best conditions and we applied this to the synthesis of **384** on a 100 mg scale in a round bottom flask, achieving a much improved yield of 77% (Scheme 3.14). Moreover, we were able to show that it was effective for the transformation of **388**·HCl into **389** in an 80% yield.

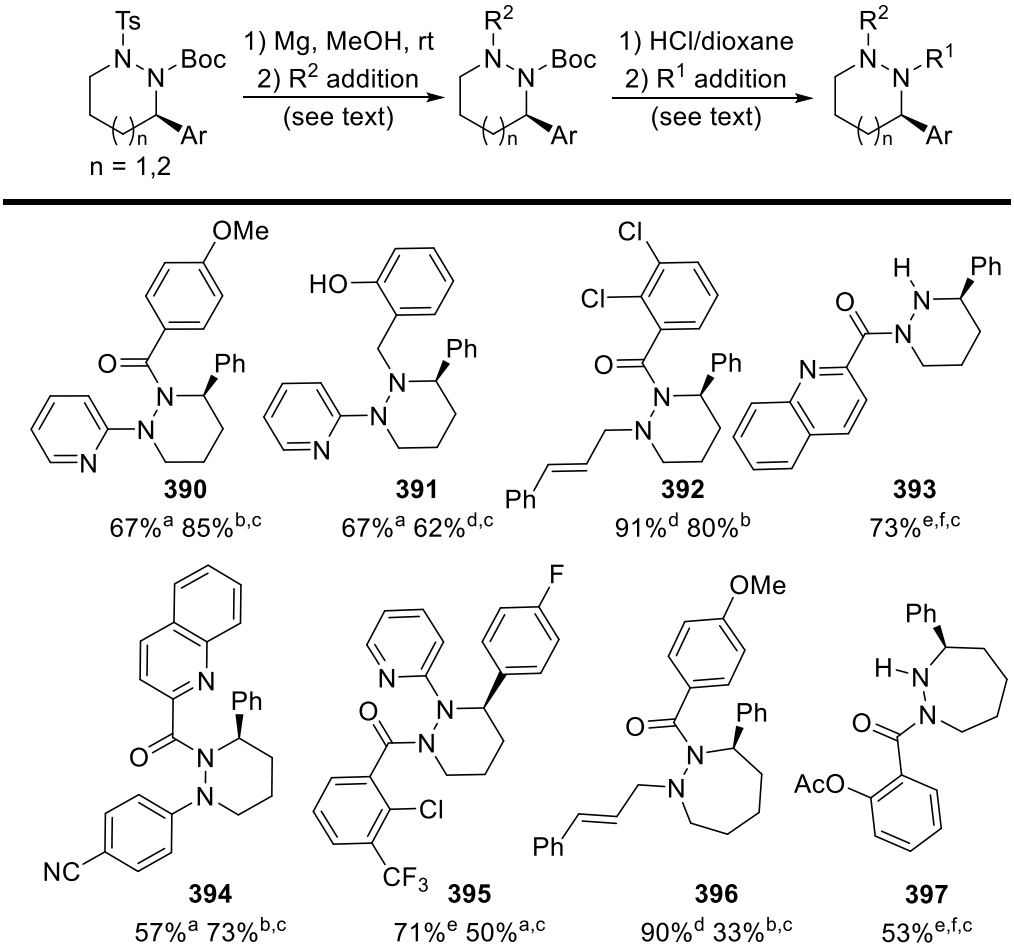


Scheme 3.14 Synthesis of **384** and **389** using optimised Buchwald-Hartwig reaction.

These findings highlight the power of high throughput catalyst screening technologies for challenging cross couplings. In the case of **384**, it enabled us to improve our initial yield approximately 15-fold (from 5% in Scheme 3.13 to 77% in Scheme 3.14).

3.3 Functionalisation of Hexahydropyridazines and Diazepines

Having extensively optimised the functionalisation of pyrazolidines, we next used this methodology on hexahydropyridazines and diazepines (Scheme 3.15). This work was mainly completed by Dr Stefan Roesner and clearly demonstrated that larger ring sizes could broadly be functionalised in a similar manner. In order to test the suitability of the deprotection and functionalisation chemistry that had been developed for pyrazolidines, we used Ts and Boc protected substrates **332-334**. These were chosen as we had already determined that Ts and Boc protected pyrazolidine **308** was the best substrate, so we used analogous systems for the larger ring sizes. This allowed us to use an identical iterative deprotection and functionalisation strategy.



Scheme 3.15 Synthesis of functionalised hexahydropyridazines and diazepines [a]ArBr, $Pd(OAc)_2$, Xantphos, NaO*t*Bu, toluene, 90 °C, 20 h. [b]RCOCl, DIPEA, CH_2Cl_2, 0 °C to rt, 18 h. [c]Synthesised by Dr Stefan Roesner. [d]RCHO, $NaBH(OAc)_3$, THF, rt, 20 h. [e]RCOCl, CH_2Cl_2, rt, 18 h. [f]Yield over three steps after Boc removal.

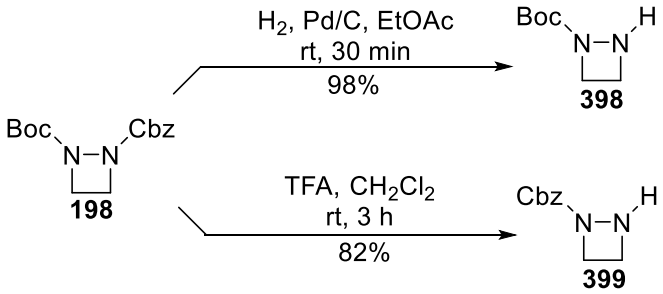
It was particularly notable that both hexahydropyridazine **393** and diazepine **396** were found to be stable after deprotection to the amine, which was not observed for any pyrazolidine examples. Clearly the larger ring sizes are significantly less prone to oxidation type processes which occured so readily for pyrazolidines. This is possibly due to the conformation of these larger rings, they might be in a less favoured conformation for the required elimination. The Buchwald-Hartwig reaction also required less optimisation for these larger ring sizes, with palladium acetate and Xantphos being effective for all of the transformations tested. Pd-170 and Pd-180 were both tested but were found to be ineffective for multiple transformations, which demonstrates their high specificity for pyrazolidines, they are clearly very sensitive to changes in ring

size. The reductive amination and acylation reactions that had previously been developed required no further optimisation and were equally as effective on these larger ring sizes.

A total of sixteen cyclic hydrazines were produced which were derivatised on both nitrogens using the methods developed herein. For four of these examples (**380**, **384**, **390** and **396**), we confirmed that racemisation did not occur by comparison of their ee by HPLC before and after N-functionalisation.

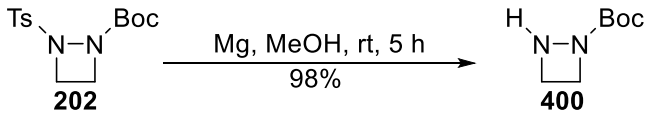
3.4 Functionalisation of Unsubstituted Diazetidines.

The final cyclic hydrazines we attempted to functionalise were the diazetidines, which we expected to be challenging substrates due to their lack of stability in comparison to the other cyclic hydrazines. Initial work was focused on simple orthogonally protected systems **198** and **202**. This allowed us to investigate the deprotection and functionalisation of these substrates. Synthesis of both diazetidines **198** and **202** was completed on a gram scale, allowing the opportunity to investigate multiple deprotection strategies. For diazetidine **198**, both protecting groups were orthogonally removed in high yields to generate amines **398** and **399** using standard procedures (Scheme 3.16).



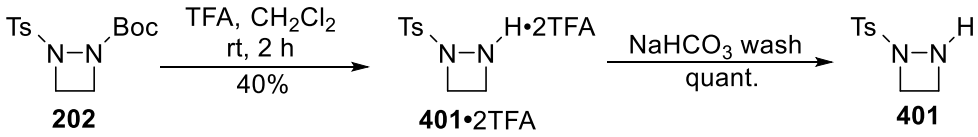
Scheme 3.16 Removal of the Boc and Cbz groups of **198**.

For diazetidine **202**, deprotection of the tosyl group using magnesium in methanol to give amine **400** was completed in excellent yield (Scheme 3.17).



Scheme 3.17 Removal of the Ts group of **202**.

For diazetidine **202**, the Boc group was also removed using TFA, and the resulting salt **401**•2TFA was purified and fully characterised (Scheme 3.18). The TFA salt was subsequently converted to amine **401** in quantitative yield by washing with saturated sodium hydrogen carbonate solution. This work suggests that diazetidines without a carbamate group are more prone to decomposition than those that possess one.



Scheme 3.18 Removal of the Boc group of **202** via TFA salt **401•2TFA**.

The TFA salt proved prone to decomposition when stored at room temperature for prolonged periods. The decomposition product could possibly be from C-N bond cleavage, as shown by the ^{1}H NMR of partially decomposed **401**•2TFA which suggests a linear amine has been formed (Figure 3.4). However, we were unable to isolate and characterise the compound, so the exact structure has not been conclusively determined.

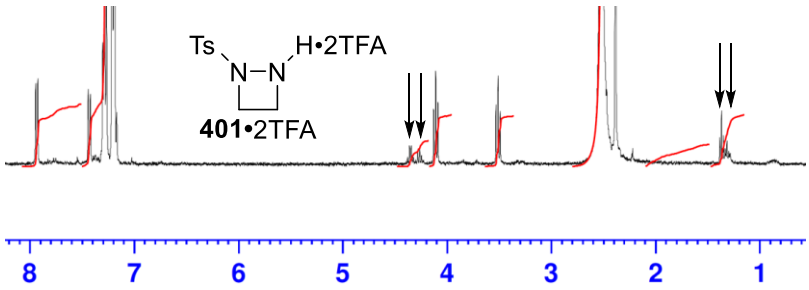


Figure 3.4 NMR of **401**•2TFA at t = 26 d. Marked peaks show the newly formed product.

Attempts to obtain a crystal structure of amine **401** were not successful, however a structure for **401**•2TFA was successfully acquired. This showed that two TFA molecules co-ordinate to the diazetidine (Figure 3.5), which is unusual as normally only one TFA anion co-ordinates to the amine. As one of the nitrogen's is now an ammonium salt measuring information about the conformation of this substrate is less meaningful. We cannot measure a meaningful torsion angle for this example as the amine is quaternised, however

we can see that for this example the extent of pyramidisation for the other nitrogen is significantly lower than for diazetidines **275** and **212**.

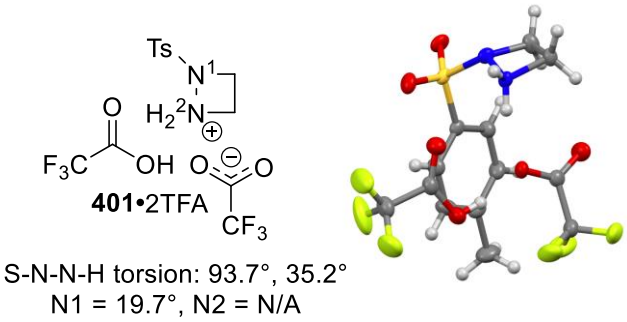
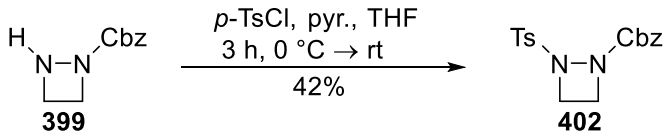


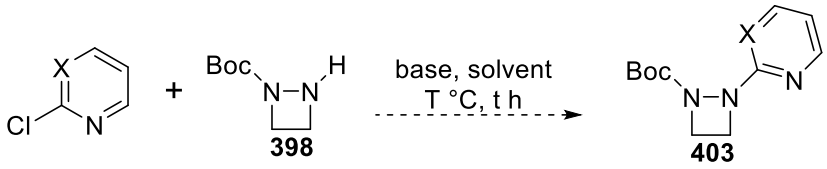
Figure 3.5 Crystal structure of **401**•2TFA.

Functionalisation of these diazetidines proved to be a significant challenge. Initially, we attempted a simple tosylation reaction to give orthogonally protected diazetidine **402**. The yield, however, was modest for this transformation (Scheme 3.19).



Scheme 3.19 Tosylation of **399** to give **402**.

Next, we attempted an S_NAr reaction to install a pyridine or pyrimidine substituent. Despite trying different combinations of bases and solvents we were unable to isolate **403** (Table 3.2). Initially we used mild conditions based on similar work on the S_NAr of an azetidine substrate.[119] These conditions however were not successful and such mild conditions are typically not used for S_NAr reactions (entries 1 and 2), with starting material recovered in both cases. Before we attempted further transformations, a test reaction from the literature was performed, the reaction of 2-chloropyrimidine and diethylamine.[120] The conditions in entry 3 gave the expected product in 80% yield. However, this did not translate successfully to the diazetidine and instead led to a complex mixture of products. The use of other conditions also led to the formation of complex mixtures (entries 4-6).

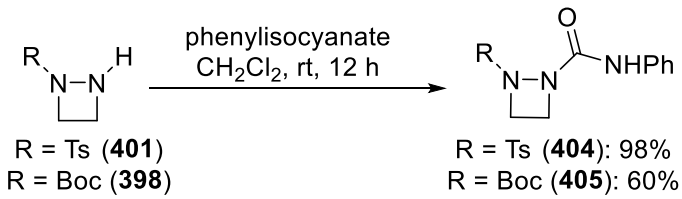


Entry	X	Base	Solvent	t / h	T / °C	Result
1	C	Na_2CO_3	1,2-DCE	12	rt	**398**
2	C	CsF	CH_3CN	24	rt	**398**
3	N	CsF	CH_3CN	8	75	Mixture
4	N	CsF	DMSO	24	rt	Mixture
5	N	CsF	DMSO	24	75	Mixture
6	N	CsOAc	DMSO	24	90	Mixture

Table 3.2 Attempted S_NAr using **398** to give **403**.

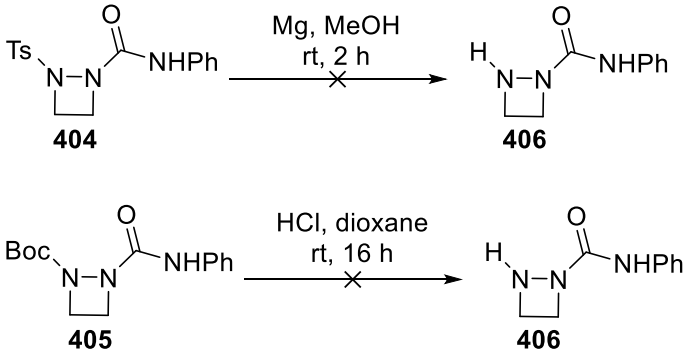
Further development of the S_NAr reaction with cyclic hydrazines was undertaken by MChem student Scott Phillips during his research project within the group. He used pyrazolidine **308** as his starting point as we believed this would be more stable and less prone to decomposition than a diazetidine under the harsh S_NAr conditions. He was ultimately unsuccessful, despite trying a wider range of substrates and conditions than those reported above.

We were however able to react amines **401** and **398** with phenylisocyanate, which gave **404** and **405** in good yield (Scheme 3.20). Although phenylisocyanate is a particularly reactive electrophile it was still encouraging to see that it is possible to functionalise deprotected diazetidines effectively.



Scheme 3.20 Reaction of **401** and **398** with phenylisocyanate to give **404**-**405**.

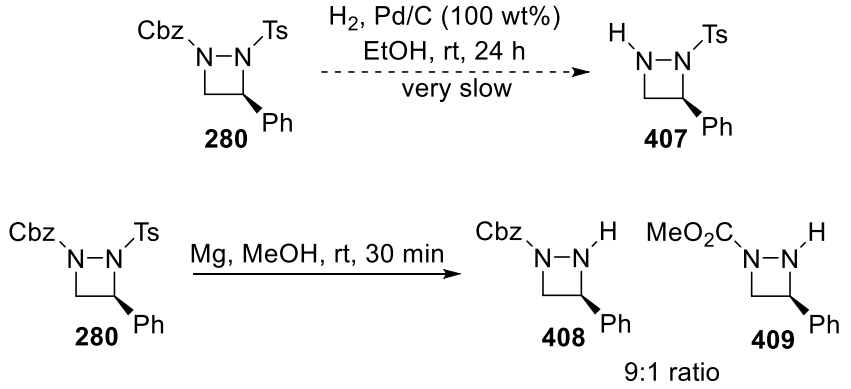
Attempted removal of the Ts group from **404** using magnesium in methanol was unsuccessful, leading to a complex mixture of products. Similarly, attempts to remove the Boc group of **405** were also unsuccessful (Scheme 3.21).



Scheme 3.21 Attempted deprotection of **404** and **405**.

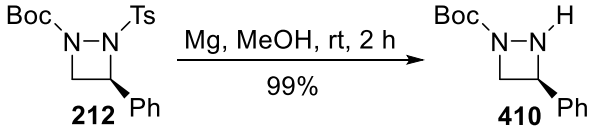
3.5 Functionalisation of C3-Substituted Diazetidines

After some promising preliminary results for the deprotection and functionalisation of unsubstituted diazetidines, we next turned to the C3-substituted diazetidines, which were expected to be amenable to similar synthetic strategies. Initially, we focused on Cbz and Ts protected diazetidine **280** as most of our available substrates had this combination of protecting groups. However, this proved to be a poor choice, as it was for pyrazolidine **306**, as neither the Ts or the Cbz group could be cleanly removed (Scheme 3.22). Using palladium on carbon to remove the Cbz group by hydrogenation to **407** proceeded extremely slowly, even with 100 weight% loadings of palladium on carbon. Using magnesium in methanol removed the Ts group again led to the transesterification of the Cbz group, forming a mixture of **408** and **409**. The ratio depended strongly on reaction time, but at a reaction time of 30 minutes methyl ester **409** was still seen as a 10% impurity and at long reaction times of 24 hours this increased to approximately 50%. Neither compound could be cleanly isolated by column chromatography, as both were prone to decomposition.



Scheme 3.22 Attempted deprotection of **280**.

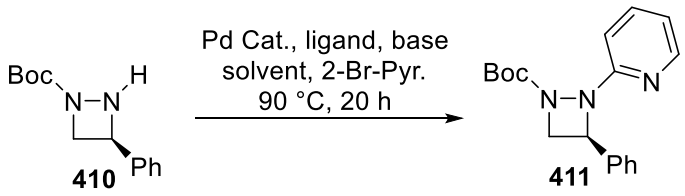
Given the results we had previously obtained for the pyrazolidine examples (Scheme 3.2) we decided instead to focus on diazetidine **212**, which had Ts and Boc protecting groups. Removal of the Ts group on this substrate proceeded without issue to give amine **410** in near quantitative yield (Scheme 3.23).



Scheme 3.23 Ts removal on **212** to give **410**.

Optimisation of this cross coupling proved to be challenging (Table 3.3). The protecting groups on diazetidine **212** are transposed relative to those of pyrazolidine **308**, so this cross coupling is on the more hindered nitrogen atom. We screened a variety of catalysts, ligands, bases and solvents, and initial analysis of the crude reaction mixtures by GCMS showed two promising results (entries 1 and 4). Both GCMS traces showed only one significant peak which had a mass corresponding to **411**, however when isolation was attempted the yield never surpassed 41%. This is possibly due to decomposition of amine **410** into smaller and more volatile components under the harsh reaction conditions. Volatile compounds would elute during the void time at the start of the GCMS run so would not be observed in the trace. It is also possible that polymeric by-products were formed, which would not be sufficiently volatile to be observed. Palladium acetate and Xantphos with sodium *tert*-butoxide had been particularly

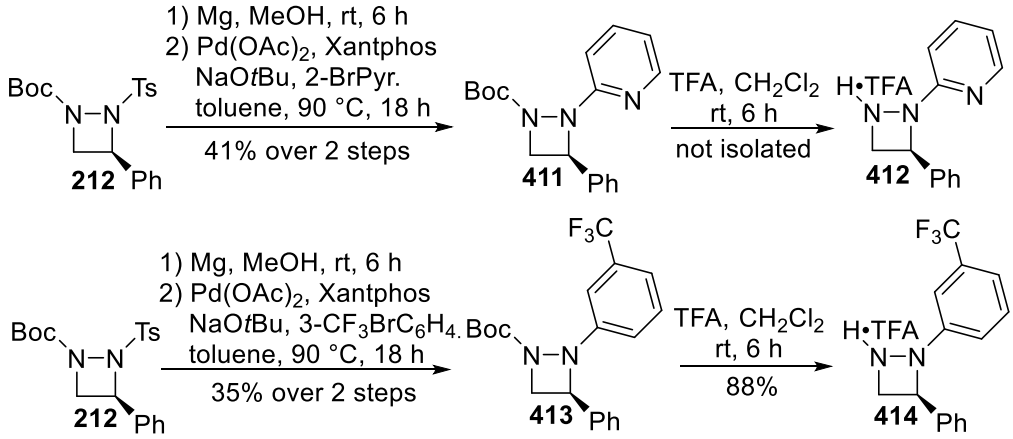
effective previously, and again they were the best conditions that we identified, although the isolated yield was significantly lower here.



Entry	Conditions	Result (%Yield)
1	$Pd(OAc)_2$, Xantphos, NaO*t*Bu, toluene	**411** (41)
2	$Pd(OAc)_2$, Xantphos, Cs_2CO_3, toluene	Complex mix
3	$Pd(OAc)_2$, Xantphos, NaO*t*Bu, dioxane	Complex mix
4	$Pd_2(dba)_3$, Xantphos, NaO*t*Bu, toluene	**411** (35)
5	$Pd(OAc)_2$, *t*BuXphos, NaO*t*Bu, toluene	Complex mix
6	$Pd(OAc)_2$, Johnphos, NaO*t*Bu, toluene	Complex mix
7	$Pd(OAc)_2$, dppf, NaO*t*Bu, toluene	Complex mix
8	$Pd(OAc)_2$, dppf, Cs_2CO_3, toluene	Complex mix
9	$Pd_2(dba)_3$, dppf, Cs_2CO_3, dioxane	Complex mix

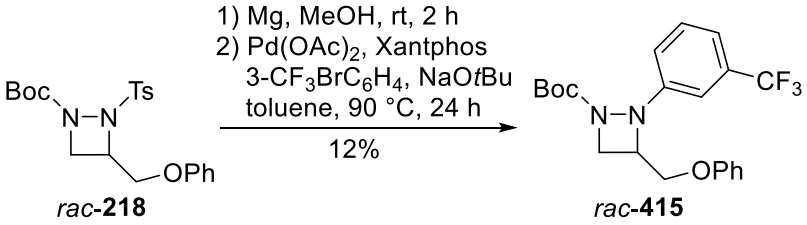
Table 3.3 Optimisation of the Buchwald-Hartwig coupling of **410**.

Next, we explored the removal of the Boc group. This proved to be surprisingly challenging, with decomposition when we attempted to isolate either **412•**TFA or the amine **412** after treatment with saturated sodium hydrogen carbonate solution (Scheme 3.24). In contrast, diazetidine **413**, which was synthesised using the same methodology was sufficiently stable to be deprotected and isolated as **414•**TFA, although it was also not stable as amine **414**.



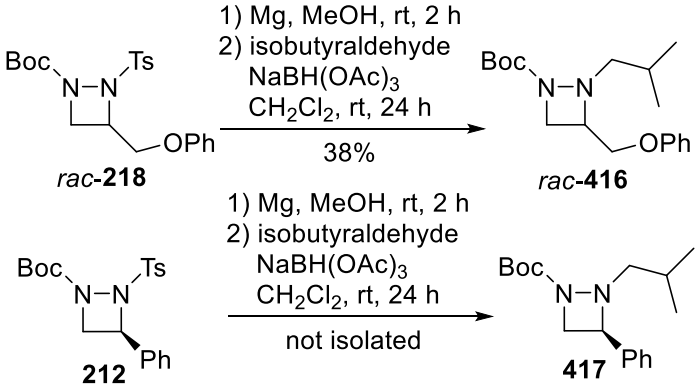
Scheme 3.24 Synthesis of **411** and **413** and attempted deprotection to their TFA salts.

Subjecting glycidyl phenyl ether substituted diazetidine *rac*-**218** to the cross coupling conditions yielded *rac*-**415**, in a very modest 12% yield over 2 steps (Scheme 3.25). Further attempts to optimise this reaction were not attempted.



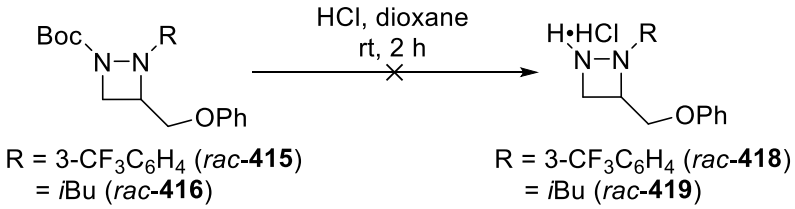
Scheme 3.25 Cross coupling of *rac*-**218** to give *rac*-**415**.

We were also able to functionalise *rac*-**218** by reductive amination with isobutyraldehyde to give *rac*-**416**, again in modest yield. Curiously, the same transformation was not successful using diazetidine **212**, the expected mass of **417** was seen on LCMS, but we were unable to isolate it (Scheme 3.26).



Scheme 3.26 Reductive amination of *rac*-**218** and **212**.

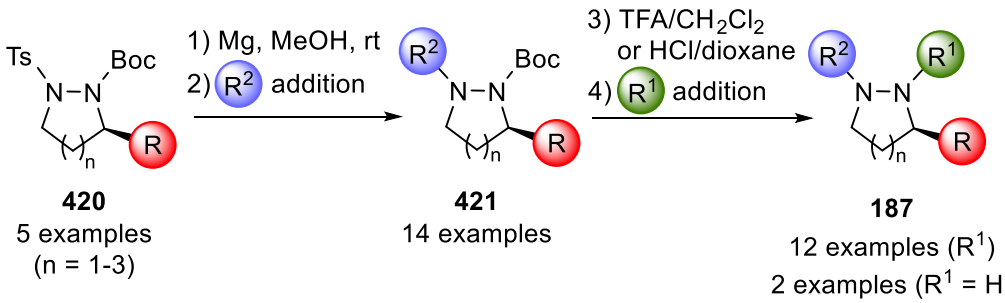
Attempts to deprotect *rac*-**415** and *rac*-**416** were not successful with HCl in dioxane, and instead led to the formation of complex mixtures of by-products (Scheme 3.27).



Scheme 3.27 Attempted deprotection of *rac*-**415** and *rac*-**416**.

3.6 Conclusions

We have shown that it is possible to derivatise a selection of the cyclic hydrazines synthesised in Chapter 2, by employing a sequential deprotection and functionalisation strategy involving the removal of Boc and Ts groups. This was achieved on of the ring sizes we synthesised and was also shown to be tolerant of changes to the C3 aryl group. Overall we synthesised fourteen examples, twelve of which had two functional groups installed sequentially and two of which had one functional group installed and the second protecting group removed (Scheme 3.28). We succesfully used three common nitrogen functionalisation chemistries: Buchwald-Hartwig cross coupling, reductive amination and acylation reactions. These were all chosen as they are frequently used in the synthesis of lead compounds in medicinal chemistry.



Scheme 3.28 Summary of functionalisation reactions for 5-7 membered cyclic hydrazines.

We extensively optimised the Buchwald-Hartwig coupling of the less hindered nitrogen of **308** by employing a high throughput screen (Scheme 3.1), we were then able to synthesise six cross coupled products in yields of up to 95%

(Scheme 3.3). Further optimisation was required for the cross coupling of biphenyl substituted pyrazolidine **312**, but this could also be achieved in an 86% yield (Scheme 3.7).

Additionally, functionalisation by using reductive aminations and acylations were also shown to be effective methods for introducing substituents on to the nitrogen. Generally these reactions required little optimisation and the transformations were achieved in up to 76% yields for reductive amination (Scheme 3.8) and up to 80% for acylation (Scheme 3.9).

Functionalisation of the more hindered nitrogen was a greater challenge, as the free amine was not stable for all pyrazolidines tested and underwent spontaneous oxidation to form the undesired achiral imine. It was found that by synthesising the HCl or TFA salt, followed by subsequent acylation in the presence of base that the desired pyrazolidines could be obtained in yields of up to 84% (Schemes 3.10-11). Buchwald-Hartwig coupling required further high throughput optimisation (Figure 3.3), but Pd-180 catalyst delivered yields of up to 80% (Scheme 3.14).

Functionalisation of diazepines and hexahydropyridazines was achieved using broadly similar methods and with similar yields, with eight examples synthesised (Scheme 3.15). They were also found to be stable as unprotected amines **393** and **397**.

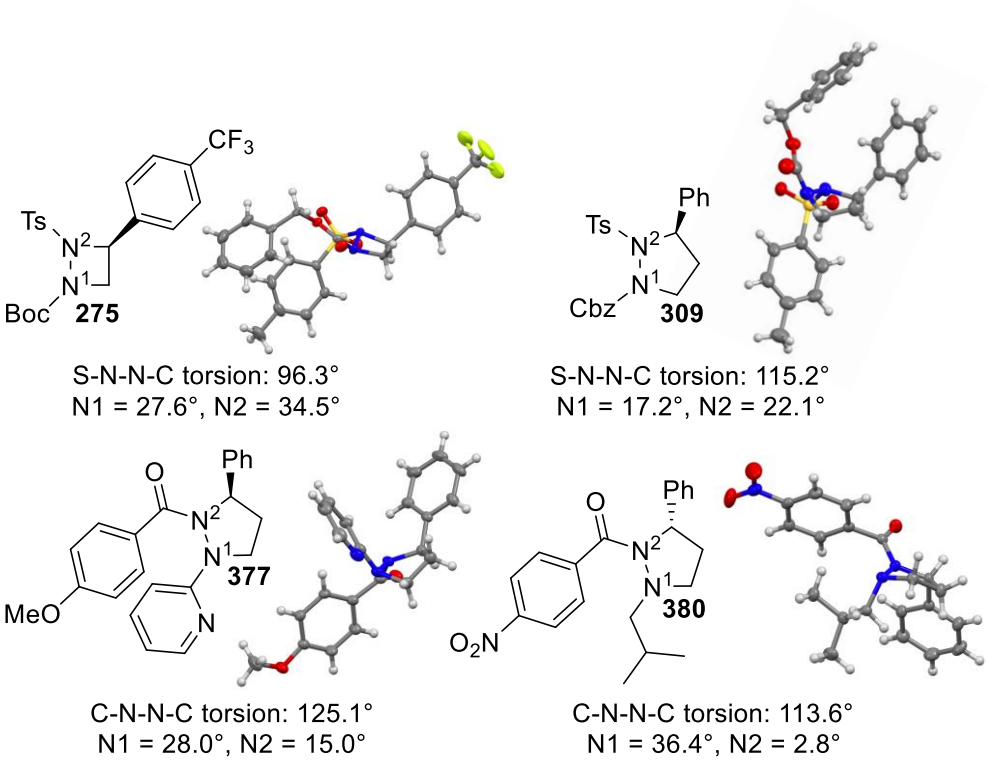
Functionalisation of diazetidines **212** and **218** was achieved by using cross couplings (Schemes 3.24-3.25) and 218 was functionalised by reductive amination (Scheme 3.26). Additionally, **198** and **202** could be condensed with isocyanates (Scheme 3.20). Attempted deprotections on these monofunctionalised substrates was unsuccessful (Scheme 3.27 and Scheme 3.21). It is likely these systems were particularly problematic due to the ring strain inherent in these systems, however full characterisation of the by-products makes it hard to analyse exactly what processes are compromising the deprotection and functionalisation chemistry.

Chapter 4: Structure & Dynamics of Cyclic Hydrazines

4.1 Crystal Structures of Cyclic Hydrazines

With the synthesis of a diverse library of cyclic hydrazines explored, we next intended to undertake further analysis to determine their conformation both in solution and solid state, and their dynamics in solution. Based on previous work in the group,[39] and previous published work (see section 1.9), we hypothesised that C3-substituted cyclic hydrazines would have a strong preference for *anti*,*anti*-**187** over the other three possible conformations (Figure 1.17).

We initially used XRD to determine the structures of diazetidine **275**, pyrazolidines **309**, **377** and **380**, hexahydropyridazine **422** and diazepine **396** (Figure 4.1). This allowed us to gain detailed information about the precise 3D structure of these compounds in the solid state. These six examples were chosen because they are representative for cyclic hydrazines of different ring sizes containing an array of different functional groups. They were also chosen as they were sufficiently crystalline to be analysed by XRD, which not all members of the library were.



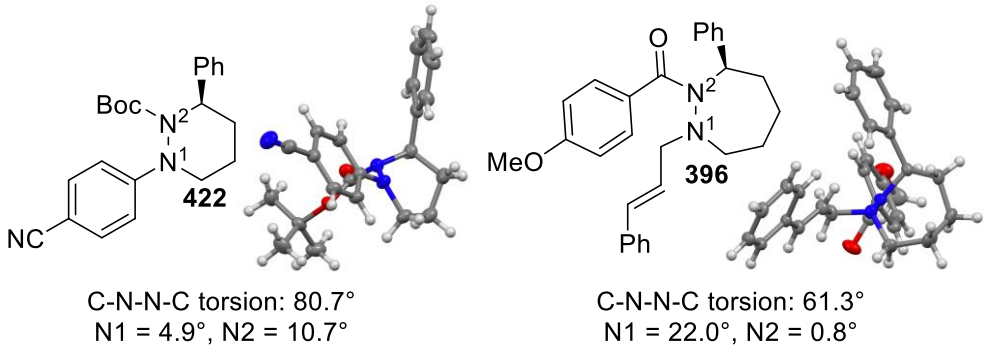


Figure 4.1 Crystal structures of cyclic hydrazines **275**, **309**, **377**, **380**, **422** and **396**.

As hypothesised all of these cyclic hydrazines adopted an *anti,anti* conformation in the solid state, regardless of ring size and functional groups. We were also able to determine other parameters using the crystal data including the extent of nitrogen pyramidisation. Unsurprisingly, smaller rings tended to have larger angles and hence more nitrogen sp^3 character, although substituent effects were also significant (particularly amide substituents which unsurprisingly displayed minimal sp^3 character). The pyrazolidines tend to have larger torsion angles between the nitrogen substituents

4.2 PMI Plots of Cyclic Hydrazine Libraries

We next turned to computational methods to analyse the library. This enabled us to analyse our entire library of functionalised cyclic hydrazines simultaneously (Figure 4.2), which we hoped would allow us to gather complementary structural data and fresh insights. It also meant we could analyse the shapes of compounds that we had not actually synthesised. To analyse this library of cyclic hydrazines we used LLAMA, which is software developed by the Nelson group at the University of Leeds.[121] This software was specifically designed to analyse the suitability of a compound in drug discovery programs, and it does this in two ways. Firstly, it assesses the 'lead-likeness' of all compounds in a library, which is done by assigning penalties for parameters like cLogP[viii] and the number of heavy atoms. Secondly, it generates PMI data which

[viii] LogP is the logarithm of the partition coefficient of a compound between *n*-ocatnol and water, also known as lipophilicity or hydrophilicity. cLogP is a

provides information about the 3D conformation. Of these we were mainly interested in the latter, as we had designed the library primarily to generate diverse 3D structures and not for lead-likeness. Most of the compounds are not defined as lead-like, we were however gratified to observe that only three of the cyclic hydrazines do not obey Lipinski's rule-of-five (**394**, **395** and **396**).[122]

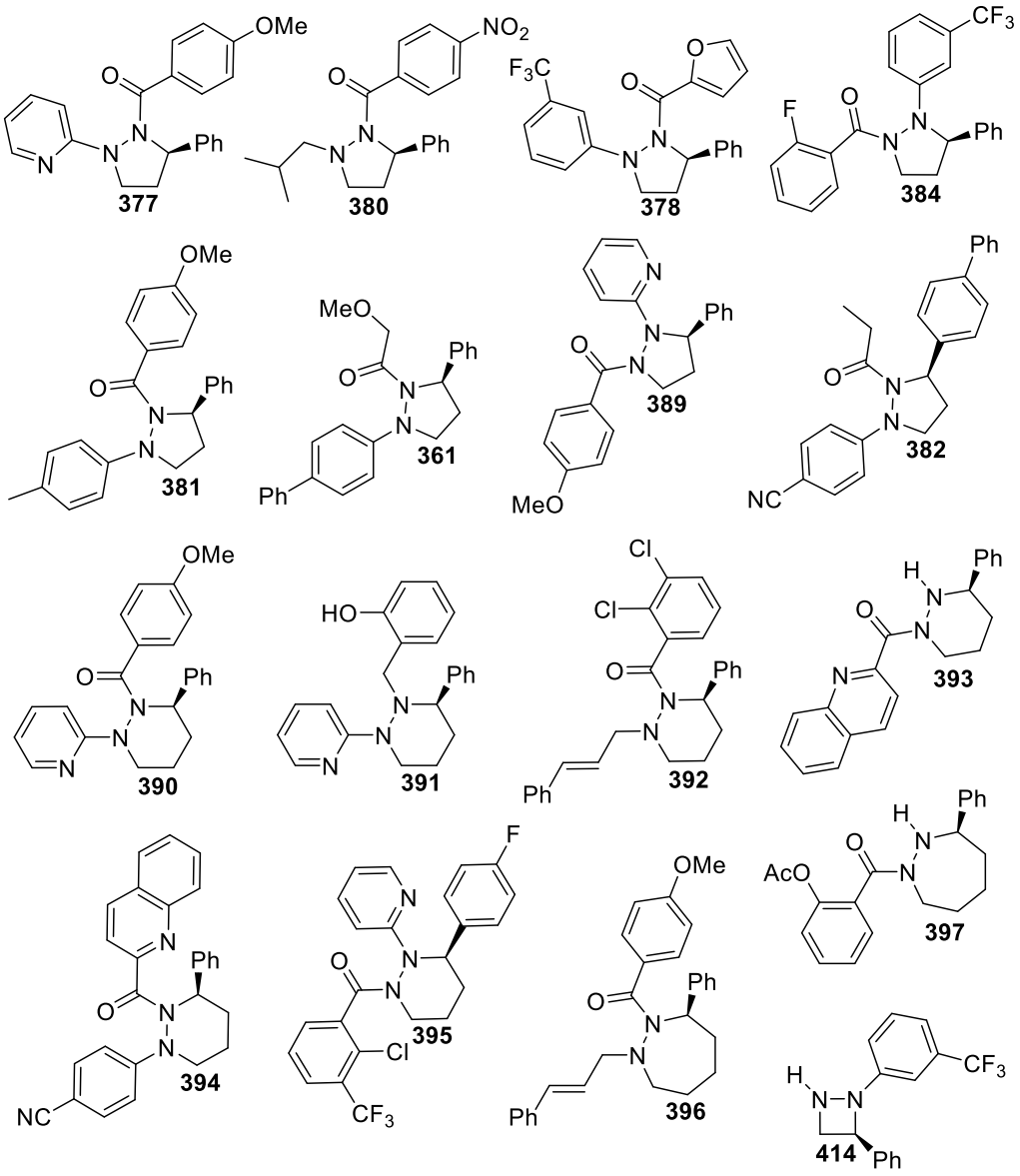


Figure 4.2 Library of cyclic hydrazines used for computational analysis.

computed version of this partition coefficient, which can be calculated using a variety of computational methods.

To calculate the PMI plot, the ground state conformer is generated using the program CORINA,[123] which has been designed to handle a broad range of organic molecules, and is widely used by pharmaceutical and chemical companies. From these structures the lowest energy conformer was taken and the moments of inertia along the x, y and z axes were calculated by the programme. The PMI I1 coordinates were calculated by dividing inertia (x) by inertia (z), while PMI I2 coordinates were calculated by dividing inertia (y) by inertia (z). This calculated data was exported from LLAMA and processed using Microsoft Excel to generate the PMI plot of the structures (Figure 4.3).

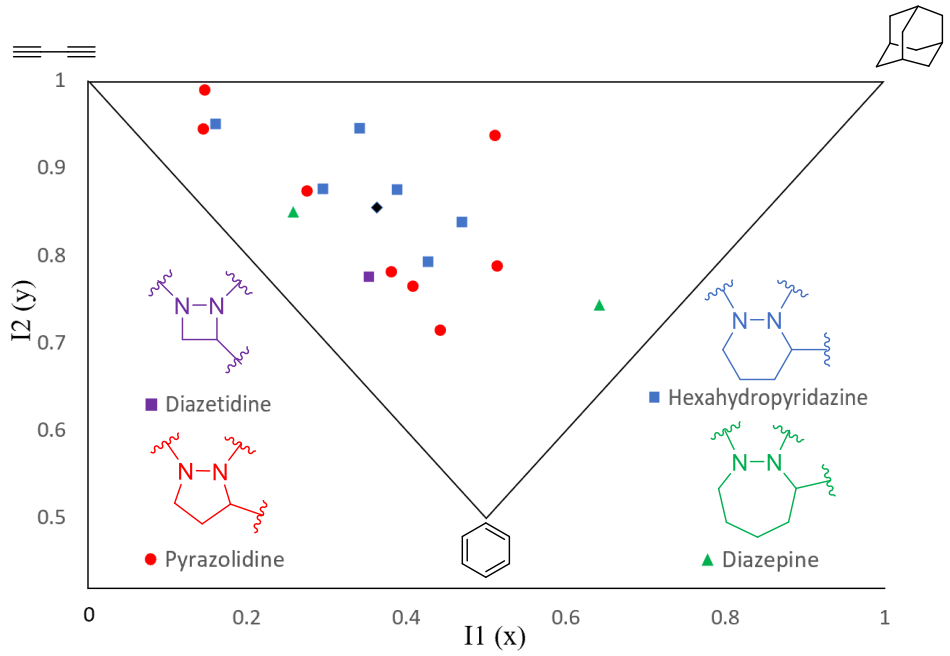


Figure 4.3 PMI plot of cyclic hydrazine library, mean PMI indicated (◆).

Significant shape diversity was observed in across the library, furthermore, no molecules were found on the left axis – which is where flatter molecules are found (Figure 1.2). Having grouped the data by ring size, no clear trends were observed, which given the modest size of the library is not surprising. Substituent effects should generally be pronounced in this type of analysis as the moments of inertia are heavily biased by heavy atoms. Our findings reveal that significant shape diversity can be introduced into the library by varying the four synthetic parameters (aryl substituent, ring size and both nitrogen substituents).

The LLAMA software also produced 3D representations of the molecules in the library, which we visualised with Mercury. This allowed us to compare the agreement between computational and XRD data. For diazetidine **275** and hexahydropyridazine **422**, overlap between the structures was good (Figure 4.4).

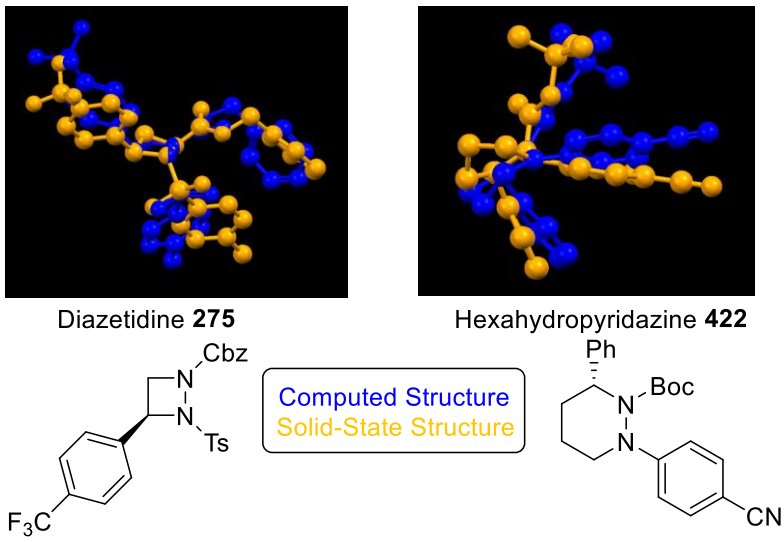


Figure 4.4 Comparison of XRD and computed structures for **275** and **422**. To generate this figure, atoms N1 and C3 of the ring are overlaid.

Other examples displayed weaker correlation between solid-state and computational structures. These included pyrazolidine **377** and diazepine **396** (Figure 4.5), although both computed and solid-state structures did adopt an *anti*, *anti* conformation. It is not clear if 5/7-membered rings are generally modelled worse by the software or if it is simply coincidence these compounds are worse.

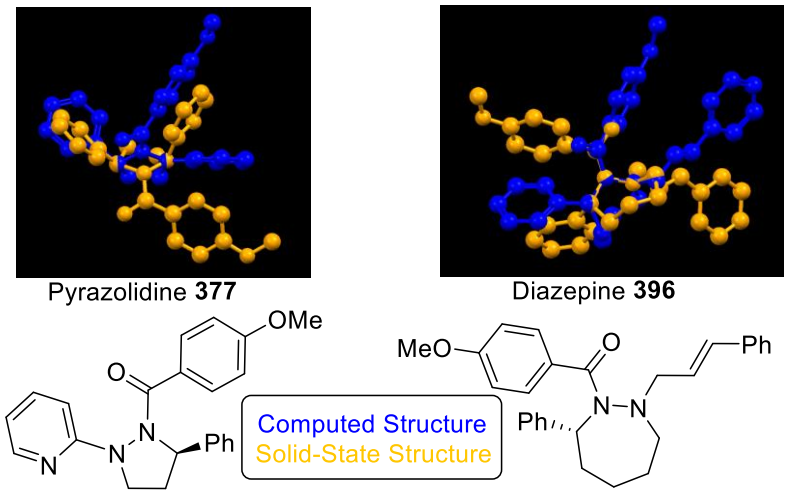


Figure 4.5 Comparison of XRD and computed structures for **377** and **396**.

Next, we expanded our LLAMA analysis to virtual libraries based on the cyclic hydrazine scaffolds. Each of the four previously synthesised ring sizes with an (*R*)-phenyl substituent were inputted and automatically functionalised on one or both nitrogen atoms with a variety of substituents, using reductive aminations, cross-couplings and acylations – as these has been used in the synthesis of our mini library. Each of the four libraries contained 256 unique functionalised cyclic hydrazines with the same set of substituents introduced across each ring size. Analysis of the average shape across the four ring sizes (Figure 4.6) provides evidence that larger ring sizes generally have increasingly spherical shapes across the series from 4- to 6- membered rings. This trend does not continue for 7-membered rings, suggesting that shape diversity does not increase significantly beyond 6-membered rings.

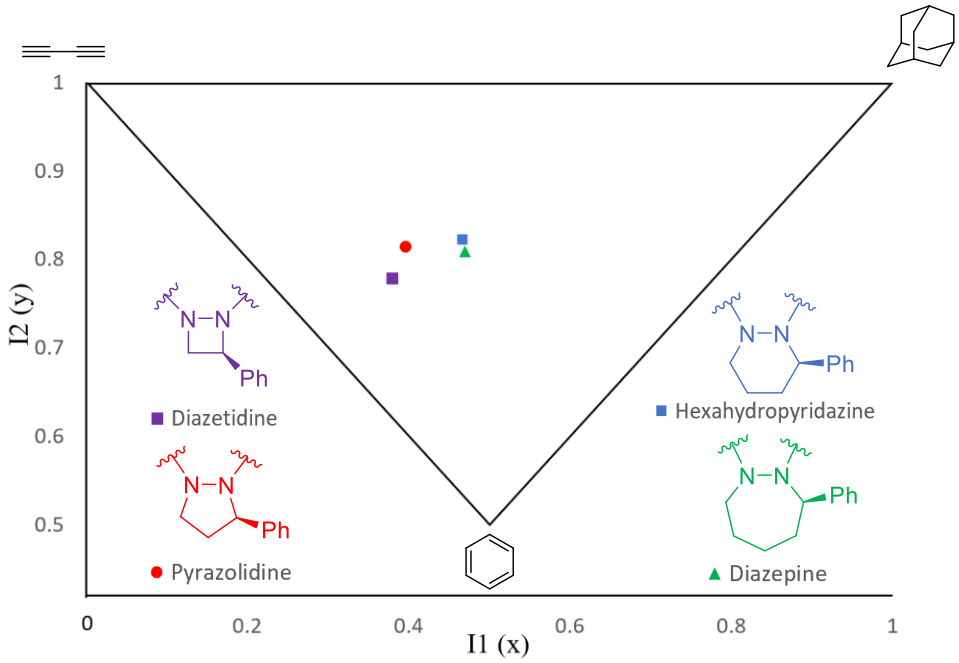


Figure 4.6 Mean PMI of computed cyclic hydrazine libraries (n = 256).

The difference between the averages is caused by greater shape diversity in the libraries of the larger ring sizes (Figure 4.7). In the diazepine library there are still a number of linear and disc-like compounds, but far more are seen in the spherical section (adamantyl-like) part of the PMI plot. Clearly the larger ring sizes lead to more diverse libraries when the same N-substituents are attached.

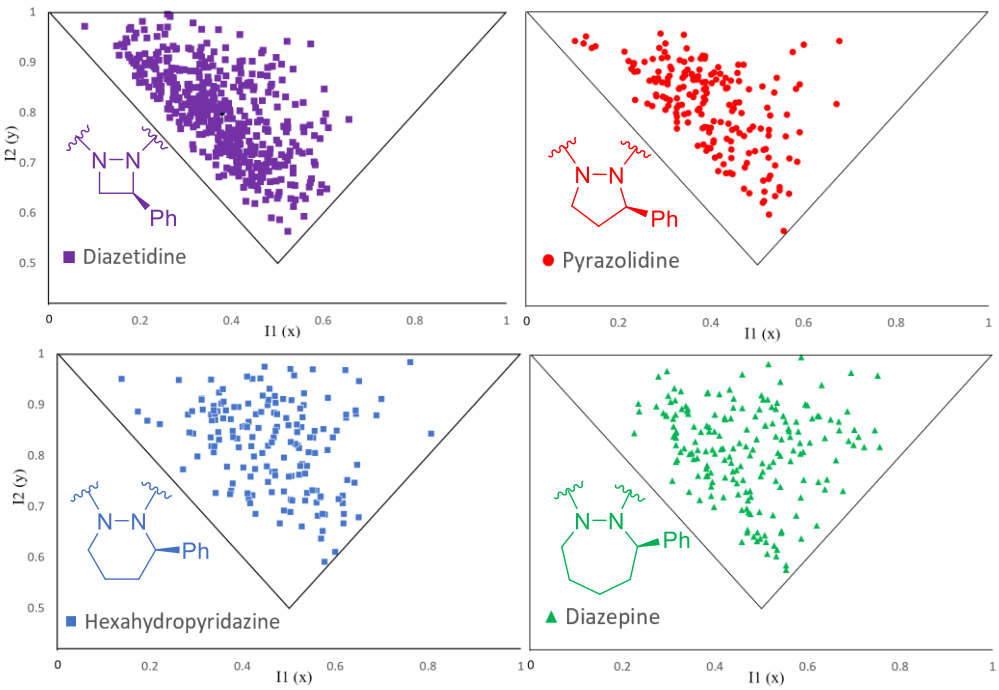


Figure 4.7 PMI plots of the four libraries analysed.

4.3 NOESY and VT NMR Analysis of Cyclic Hydrazines.

To gather information about the structure of these cyclic hydrazines in solution, we turned to NMR spectroscopy. We anticipated that this would allow us to gather solution state structural insights using NOESY and would also allow us to study the fluxional behaviour using VT NMR. The first substrate we studied was pyrazolidine **377**, which adopts the *anti,anti* conformation in the solid state (Figure 4.1). The substrate has sufficient numbers of hydrogens close to the branch points of the substituents to give us a good chance of observing NOE's between them. Complete assignment of the spectrum in $CDCl_3$ at 298 K had already been completed after the synthesis (Figure 4.8) so initially NOESY experiments were measured under these conditions. Assignment of H^8, H^{10}, H^{11} and H^{12} was done in conjunction with NOESY data (see Figure 4.9).

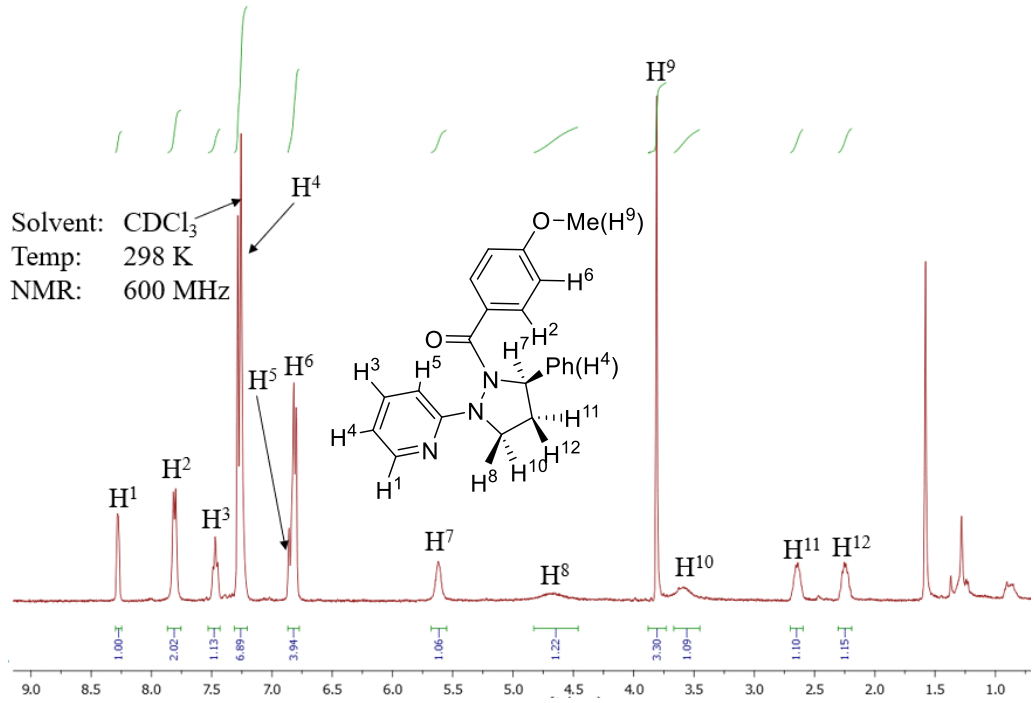


Figure 4.8 ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) of **377** with assignments.

Next, the NOESY spectrum was acquired with a mixing time of 0.9 s and several informative NOE's were observed, including from H^2 to H^7 and H^4 to H^{12} (Figure 4.9). Although these NOE's provide strong evidence for the *anti* relationship of the phenyl substituent relative to the the *para*-methoxybenzoyl substituent, no NOEs were observed from any of the pyridine protons (H^1, H^3, H^5 and H^6), which means that the position of the pyridine substituent could not be determined. Perhaps H^8 is closest to the pyridyl ring, and since it is extremely broad, the observation of cross-peaks between these groups may be difficult.

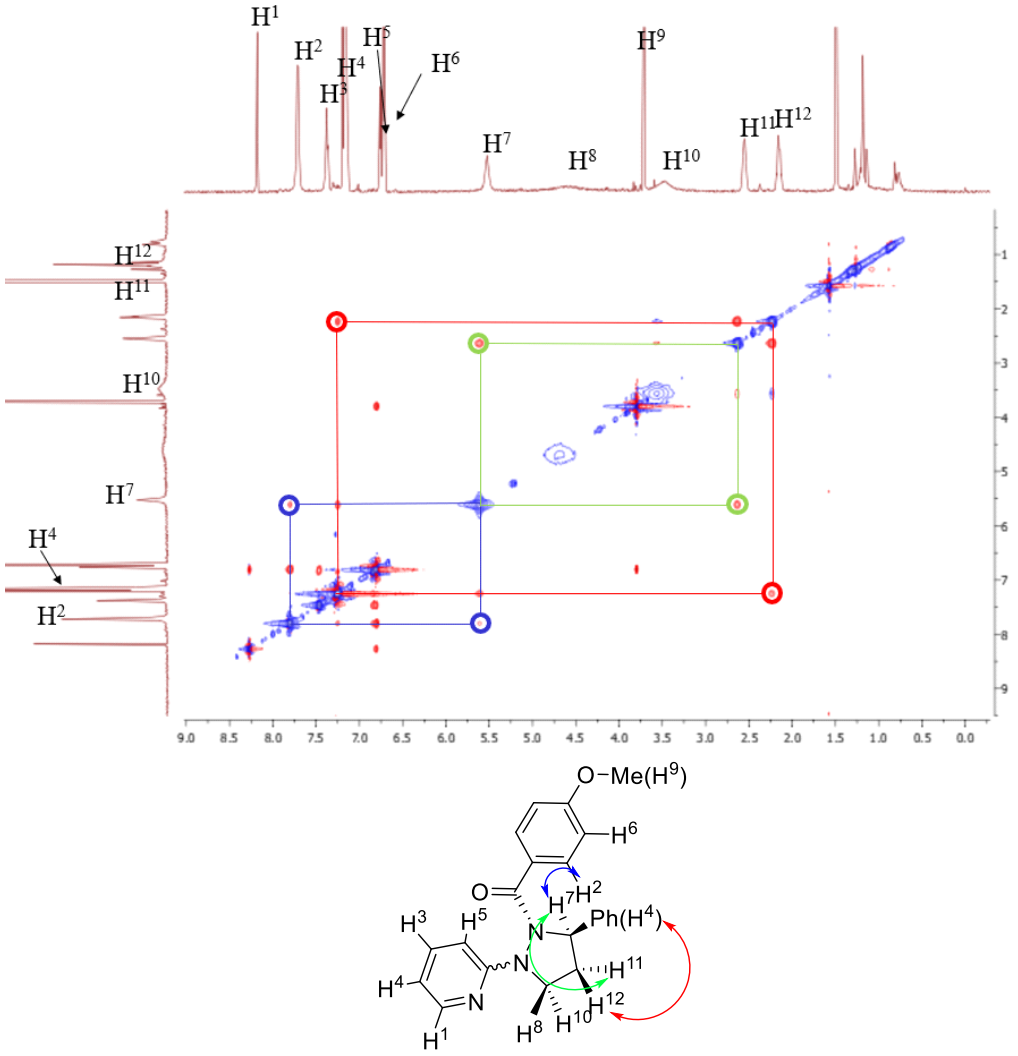


Figure 4.9 NOESY NMR (600 MHz, $CDCl_3$, 298 K) of **377**, 0.9 s mixing time.

To obtain a sharper spectrum of **377**, we used d_6-DMSO as the solvent. A sharper spectrum was observed at 333 K. However, the NOESY spectrum did not reveal any new information, as cross peaks from the pyridine hydrogens still were not seen.

Next, we cooled the sample down in order to see if we could freeze out the two or more conformers that were causing the peak broadening at 298 K. At 233 K in $CDCl_3$ the spectrum cleanly resolved into two isomers, in a ratio of 56:44, which could be further assigned using COSY and NOESY spectra (Figure 4.10). There are two possible explanations for the observation of isomers here, they

either arise from slow interconversion of two isomers arising from nitrogen inversion or amide bond rotation.

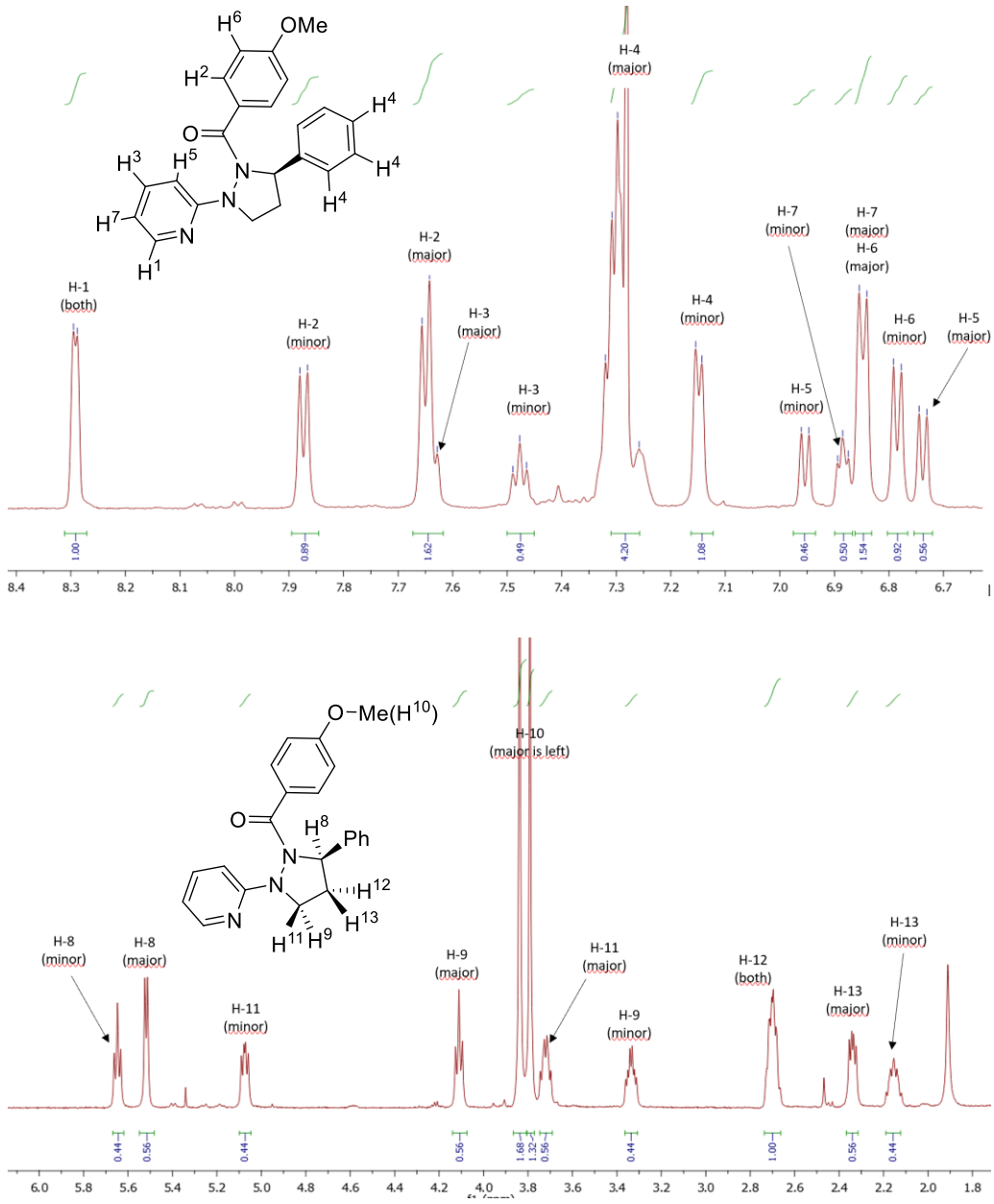


Figure 4.10 ^{1}H NMR (600 MHz, $CDCl_3$, 233 K) of **377** with assignments.

The NOESY spectrum was recorded at 233 K, with mixing times of 0.3 s and 0.6 s. With the 0.3 s mixing time, interconversion between isomers did not occur, making it possible to observe cross peaks for individual isomers. From this spectrum an interesting NOE was observed between H^2 and H^8, which was only observed for the major isomer (Figure 4.11).

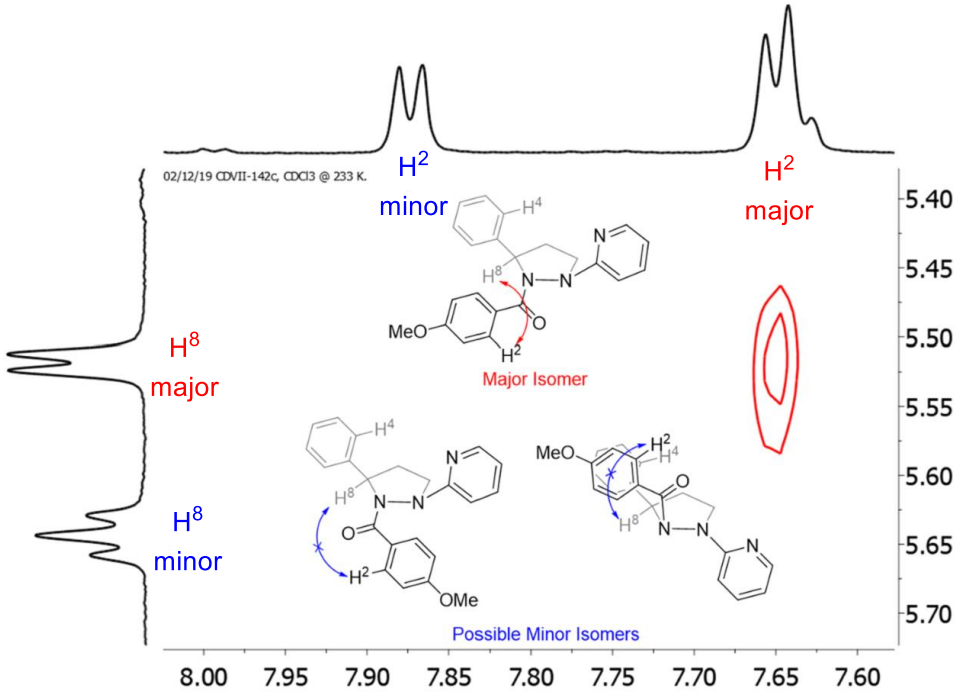


Figure 4.11 NOESY NMR (600 MHz, $CDCl_3$, 233 K) of **377**, 0.3 s mixing time.

This does not determine what the minor isomer is, as in both possible isomers you would not expect and NOE between H^2 and H^8. Again, no NOE's were seen from any of the pyridine protons. Increasing the mixing time to 0.6 s showed an NOE between H^4 and H^5, which suggests the pyridine and phenyl rings are on the same face. However, at this longer mixing time interconversion between isomers is seen, making it impossible to tell if the NOE was only occurring in the major isomer or if it occurred in the minor isomer as well. This means it was not possible to conclusively determine from this which minor isomer was present.

As we had an interconverting pair of isomers in an unequal proportion it was possible to determine the barrier to their interconversion. To do this we acquired ^1H NMR spectra from 223 K to 293 K in 10 K increments (Figure 4.12). This clearly showed the coalescence of the OMe peak.

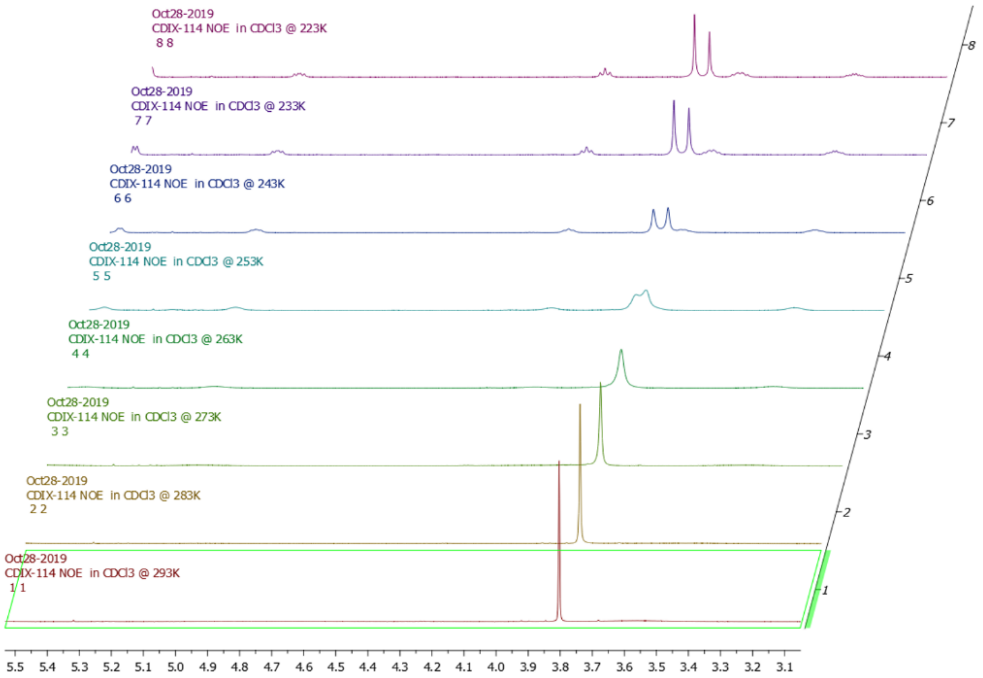


Figure 4.12 ^{1}H NMR (600 MHz, $CDCl_3$) of **377** from 223 K to 293 K.

From this we estimated the temperature of coalescence (T_C) to be 258 K. In order to determine the barrier to inversion we used Eyring's equations, modified by Shanan Atidi and Bar-Eli[124] to account for the unequal proportion of isomers (Equation 1):

$$\Delta G_A^{\ddagger} = RT_C\left[10.62 + log\frac{X}{2\pi(1-\Delta P)} + log\frac{T_C}{\Delta v}\right]$$

Equation 1

R = 4.57 cal mol^{-1} K^{-1}, T_C = 258 K, Δυ = 30 Hz (peak difference is 0.05 ppm on a 600 MHz spectrometer), $log\frac{X}{2\pi(1-\Delta P)} = -0.567$

$$\Delta G_A^{\ddagger} = 12.9\ kcal\ mol^{-1} = 54.1\ kJ\ mol^{-1}$$

Barriers to N-inversion in cyclic hydrazines are typically higher than this (Section 1.10). Amide bond rotation is generally a lower energy process in cyclic hydrazines than nitrogen inversion, as shown by Lehn and Anderson in their studies of tetrahydropyridazines.[125] This means that the relatively low barrier to inversion seen here suggests this is the more likely explanation for the origin of the two isomers. The error associated with this measurement is relatively small

at ± 1.0 kJ mol^{-1} for the coalescence temperature (with a lower bound of 253 K and an upper bound of 263 K for coalescence). There is also an error from the temperature reading of the spectrometer, however this will be significantly smaller than 5 K so it is insignificant compared with the T*c* error.

Next, we analysed cyclic hydrazine **380**, to try and get clear NOESY data that would demonstrate than an *anti*,*anti* conformation is being adopted in solution. The challenge with this substrate is that the protons on the *iso*-butyl substituent and the protons on the hydrazine ring (H^9/H^{10} and H^7/H^8) are in very similar chemical environments. After some experimentation we determined that $CDCl_3$ and d_6-acetone were unsuitable to resolve these signals, but d_6-benzene at 343 K gave a well resolved spectrum. Only one set of signals are observed under these conditions so either fast exchange is occurring or there is a single conformation (Figure 4.13).

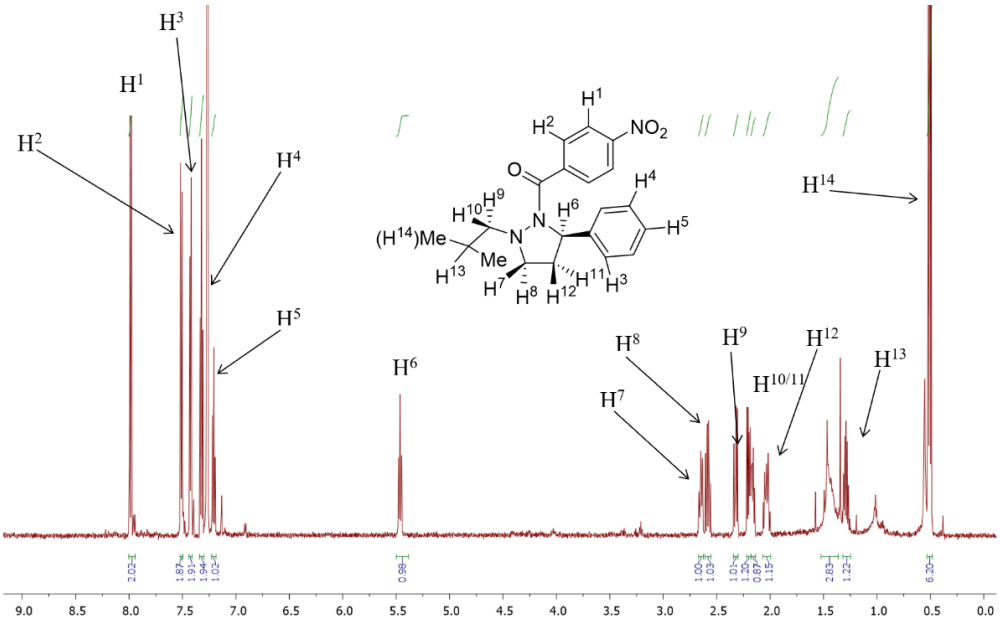


Figure 4.13 ^{1}H NMR (500 MHz, d_6-benzene, 343 K) of **380** with assignments.

The NOESY spectrum (0.6 s mixing time) showed several important NOE's. An NOE between H^6 and H^8 indicated that they are on the same face of the molecule (Figure 4.14). An NOE was also observed between H^8 and H^2, which shows that they are also on the same face. Taken together, this implies that H^6 and H^8 are on the same face of the molecule as the *para*-nitrobenzoyl substituent.

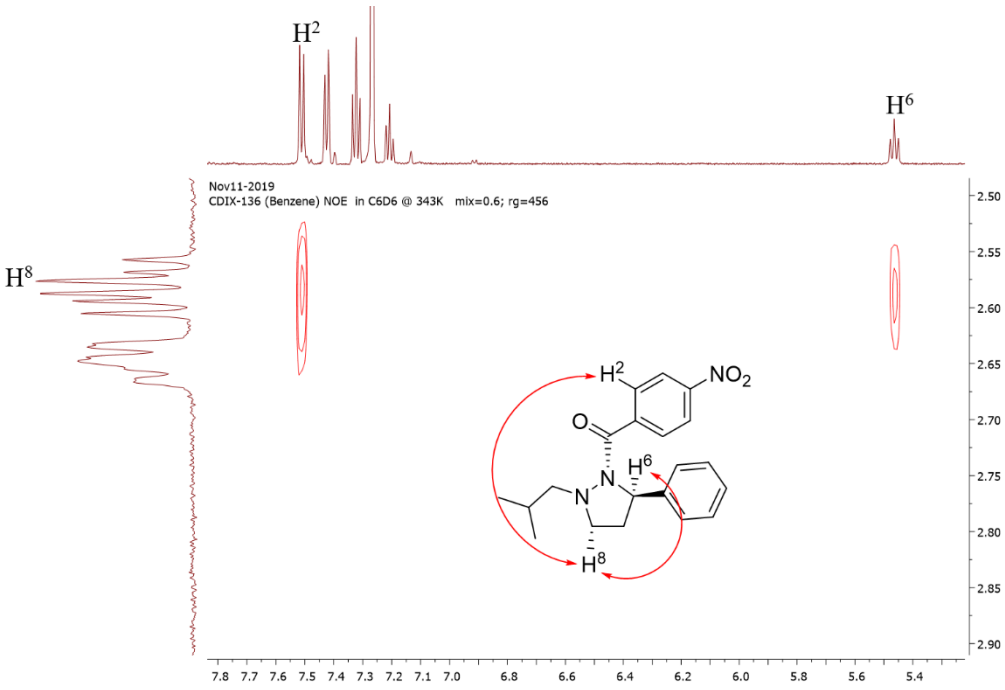


Figure 4.14 NOESY NMR (500 MHz, d_6-benzene, 343 K) of **380**, 0.6 s mixing time.

This spectrum also provided evidence for the positioning of the *iso*-butyl substituent, with NOE's seen from H^3 of the phenyl to H^9 and possibly to H^{10} (Figure 4.15).

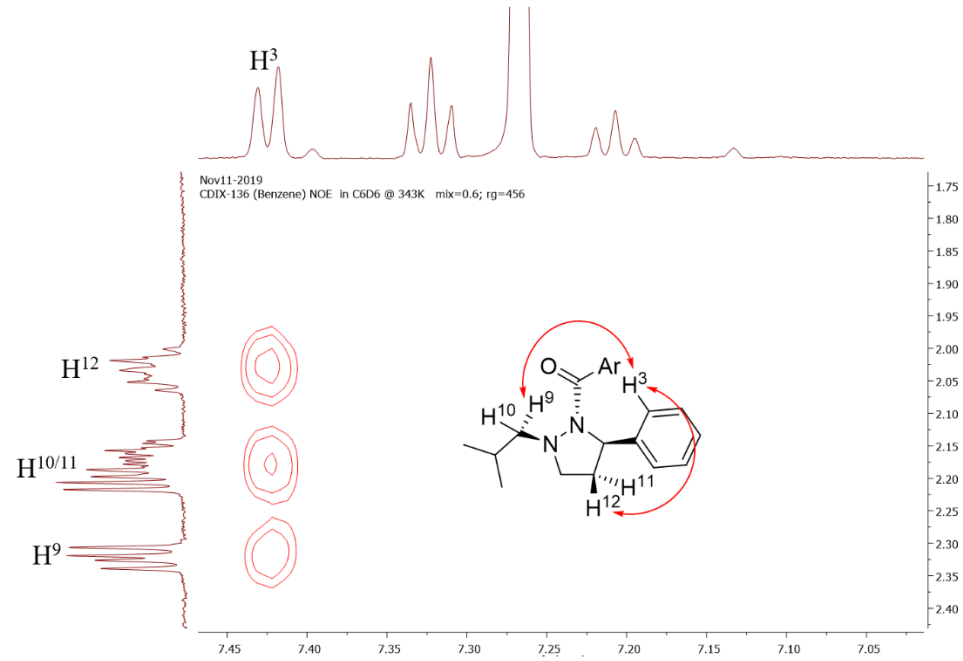


Figure 4.15 NOESY NMR (500 MHz, d_6-benzene, 343 K) of **380**, 0.6 s mixing time.

Taken together this gives clear evidence that **380** is in the *anti*,*anti* conformation in solution, under these experimental conditions. Analysis of **380** at low temperature revealed one major and two minor isomers seen at 233 K in both $CDCl_3$ and d_6-acetone in an 84:11:5 ratio (Figure 4.16). Observation of two minor isomers suggests that at least one minor invertomer is present, if we assume one is derived from amide bond rotation. Therefore, other *N*-invertomers are energetically accessible, at least for this system. Attempts to analyse the NOESY spectrum acquired at 233 K were not fruitful.

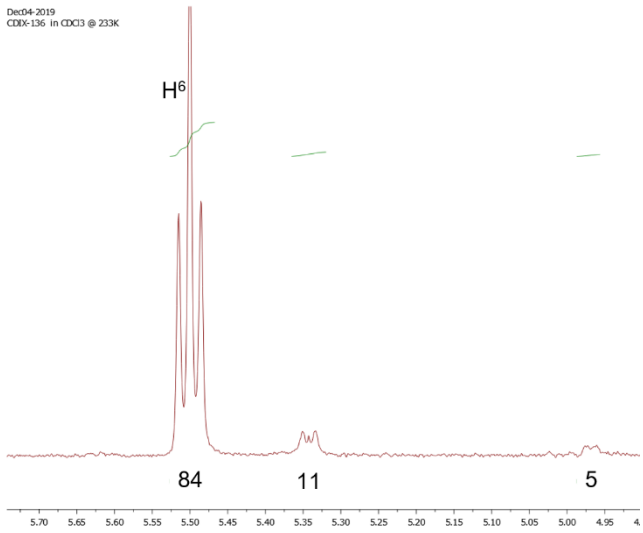


Figure 4.16 ^{1}H NMR (500 MHz, $CDCl_3$, 233 K) of **380**, showing H^6 only.

4.4 Conclusions

We have tested the hypothesis that 3-substituted cyclic hydrazines have a strong preference for the *anti*,*anti* conformation. XRD analysis of six cyclic hydrazines showed that this was adopted universally across all four ring sizes synthesised and regardless of which substituents were present. The crystal data also showed the unusually high extent of nitrogen pyramidisation in several examples (**275**, **309** and **377**), suggesting the conformational restraints imposed by the system are overcoming the normally strong preference for sp^2 hybridised amide bonds.

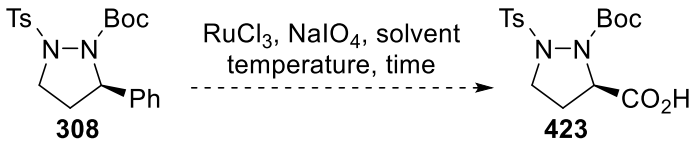
Computational analysis using LLAMA generated a PMI plot of the library of synthesised cyclic hydrazines. This showed the library we had synthesised

contained significant shape diversity and did not contain any molecules that are defined as flat by PMI analysis. Further analysis of virtual larger libraries generated by the program of phenyl-substituted diazetidines, pyrazolidines, hexahydropyridazines and diazepines revealed that shape diversity increases with ring size, up to 6-membered rings, after which no notable increase is observed. Even for the 4- and 5-membered rings, the libraries still display significant shape diversity and access a large amount of chemical space.

Analysis using NOESY showed that cyclic hydrazine **380** adopted an *anti,anti* conformation in solution, confirmed by key NOE's between the nitrogen substituents and the hydrogens on the ring. Low temperature NMR analysis of this compound showed it existed as three isomers in an 84:11:5 ratio, however resolving the structure of these compounds was not possible. NMR spectra of **377** at low temperature only showed two isomers, in a 56:44 ratio. Further analysis by VT NMR and NOESY strongly suggested that these were amide bond rotamers and not invertomers from *N*-fluxionality. The barrier to inversion was found to be 54 kJ mol^{-1}, which provided further evidence that amide bond rotation was occurring.

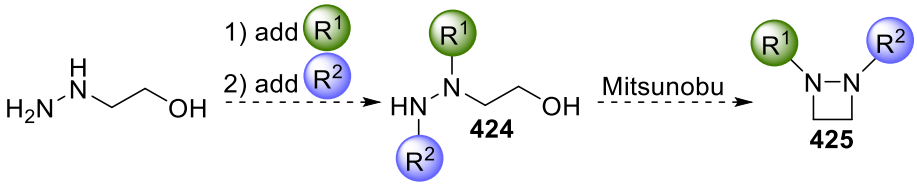
Chapter 5: Future Work

Further diversification of the aryl group would also allow us to incorporate more substituents at the C3-position. The ability to incorporate a carboxylic acid functionality would be particularly useful, as this structural feature is seen in a number of cyclic hydrazine containing natural products (Figure 1.3). This could potentially be achieved by oxidation of the aryl group using ruthenium tetroxide, which has been shown to be an effective oxidising agent for this transformation.[126-128] This synthetic methodology is currently being optimised by other members of the group, with pyrazolidine **308** chosen initially as the test substrate (Scheme 5.1).



Scheme 5.1 Proposed synthesis of carboxylic acid **423**.

It would also be desirable to further optimise the synthesis of diazetidines, particularly with alternative deprotection and functionalisation strategies. The orthogonal deprotection and functionalisation strategy attempted in chapter 3 was only partially successful with the synthesis of **414**. In order to develop this further it would be necessary to develop an alternative strategy, possibly by exploiting the regioselective protection of 2-hydrazineylethan-1-ol to form **196** (Scheme 3.1) to install functional groups instead of protecting groups to give **424** (Scheme 5.2). This could then be cyclised using the Mitsunobu reaction to give functionalised diazetidine **425**, providing R^2 is not a carbamate.



Scheme 5.2 Proposed synthesis of **425**.

These libraries would not contain a chiral centre, which would obviate the need for an enantioselective synthetic methodology to be developed. There is also evidence from LLAMA that these libraries would not need a substituent at C3 to have a diverse range of PMI co-ordinates (Figure 5.1). Although some examples are clearly flat, there are a number of much more 3D examples, and LLAMA could be used to identify and target them.

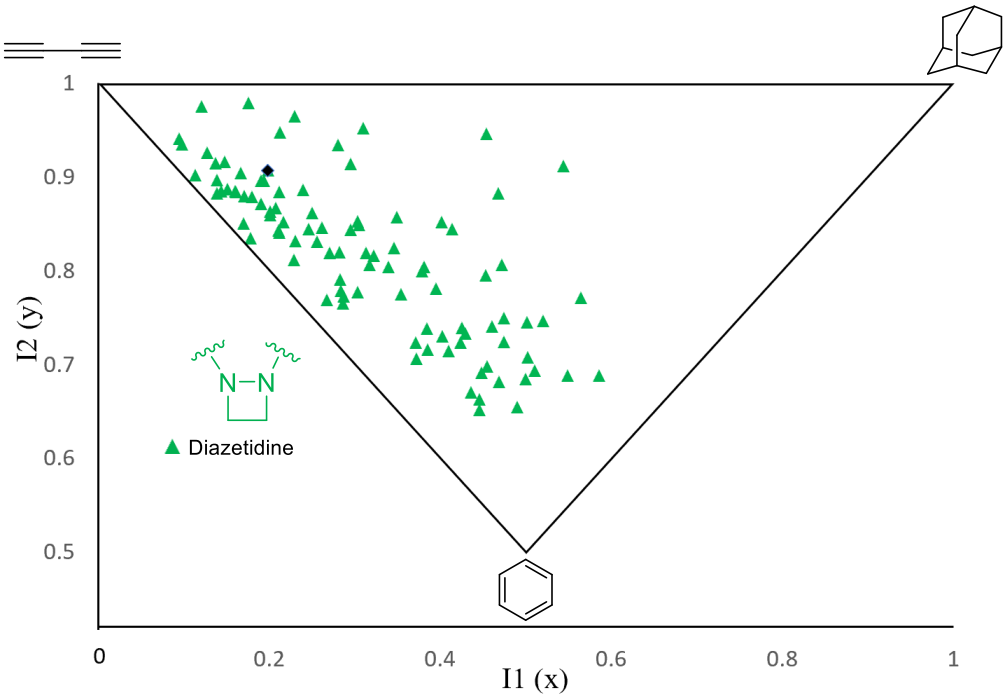


Figure 5.1 PMI plot of computed diazetidine library (n = 96), mean PMI indicated (◆).

This can also be seen when the same analysis is conducted on a hexahydropyridazine scaffold (Figure 5.2). As we previously observed for the phenyl substituted libraries (Section 4.2) there is a difference between the libraries, with the larger ring size producing a library with more shape diversity.

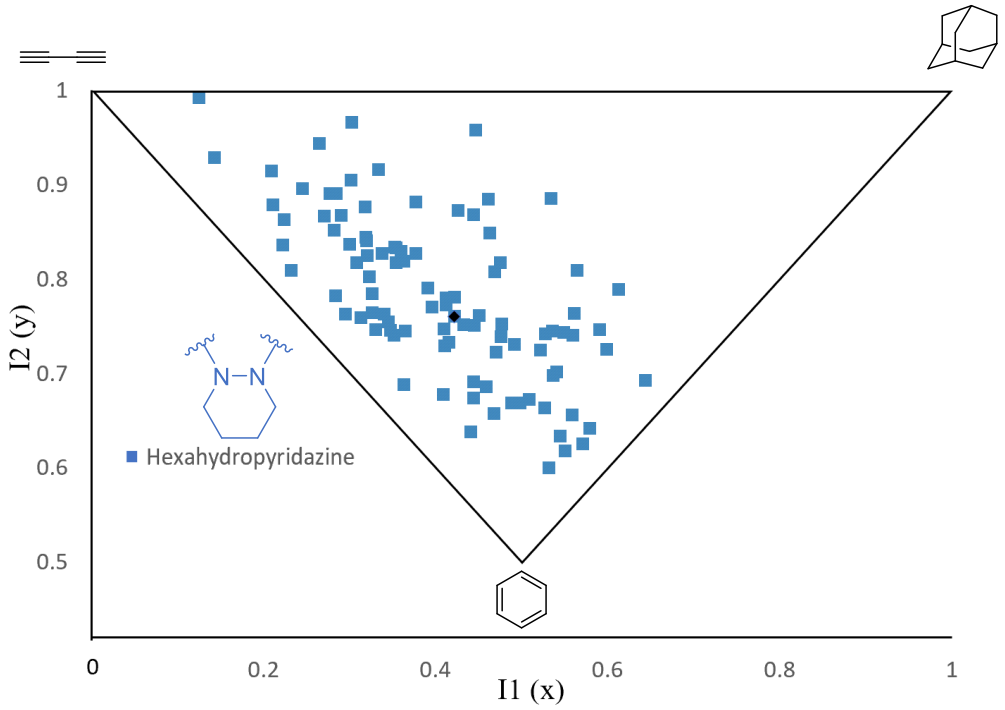
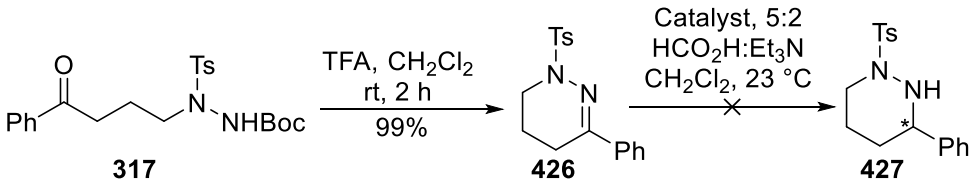


Figure 5.2 PMI plot of computed hexahydropyridazine library (n = 96), mean PMI indicated (◆).

Devising a synthetic methodology which did not require the use of the Mitsunobu reaction would be beneficial, as it has poor atom economy, requires large amounts of solvent and made purification challenging. This could potentially be achieved by synthesising cyclic hydrazones and reducing them asymmetrically to the corresponding hydrazines. We have carried out some initial studies on hydrazone **426**,[129] however our previously developed ATH methodology with catalysts **233**, **243-248** was ineffective (Scheme 5.3).

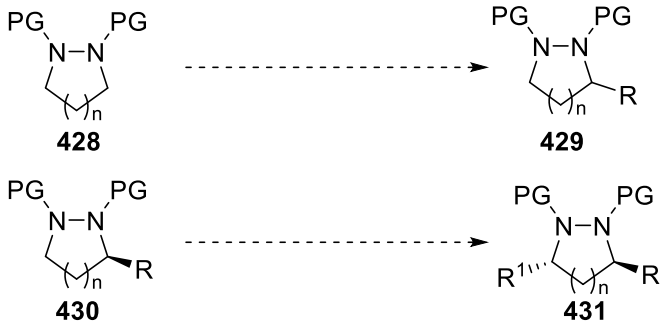


Hydrazone **426** recovered after 48 h with catalysts **233**, **243-248**

Scheme 5.3 Attempted synthesis of amine **427** from hydrazone **426**.

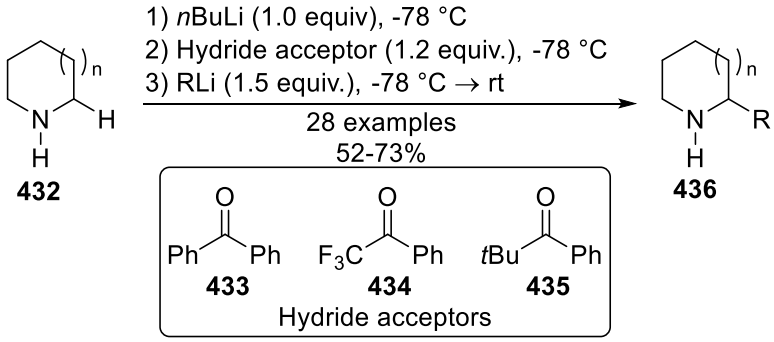
Another possible synthetic strategy we have recently considered is using C-H activation to install substituents at the 3-position of the hydrazine ring, converting **428** to **429**. This would potentially allow the introduction of a more

diverse range of substituents to the library, and it could also be used to introduce a second substituent to our existing cyclic hydrazine building blocks **430** diastereoselectively to give **431** (Scheme 5.4).



Scheme 5.4 Proposed functionalisation of cyclic hydrazines *via* C-H activation.

There has been significant recent interest in C-H activation,[130] and a number of these could feasibly be applicable to cyclic hydrazines. Recent approaches include photocatalytic methods from MacMillan[131] and Doyle,[132] and directing group based chemistry from Yu,[133, 134] all of which utilise cyclic amines as substrates. We felt however that the recent work of Seidel *et al.* outlined a strategy that had the greatest potential for our substrates.[135] They were able to functionalise a broad range of cyclic N-H amines **432** by deprotonation, followed by addition of a hydride acceptor and then the addition of an organolithium nucleophile to give **436**. They showed that this methodology was applicable to a broad range of amines and was compatible with a wide range of readily available organolithium reagents (Scheme 5.5).



R = Ph, 4-OMeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$
3-MeC$_6$H$_4$, 2-OMeC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-naphthyl, 3-naphthyl CH=CHPh
3-pyridyl, 2-thiophenyl, *n*Bu; n = 0-7

Scheme 5.5 Synthesis of functionalised cyclic amines by Seidel et al.[135]

Applying this to cyclic hydrazines would be a highly complementary approach to the ones outlined in this thesis. It would allow us to introduce substituents at the 3-position, although this would not be enantioselective. In a subsequent paper they showed that the scope of this chemistry could be expanded to include alkynes, indoles and benzofurans, which we have not yet incorporated into cyclic hydrazine scaffolds.[136]

Due to time constraints, the synthesis of RipK1 inhibitor **337** could not be completed, however further investigation is currently underway within the group. Current investigations are focused on replacement of the Ts group with a Ns group, as this can be deprotected under milder conditions.

Chapter 6: Experimental

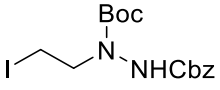
General Experimental

All reactions were performed under an atmosphere of nitrogen in oven-dried glassware unless otherwise stated. Anhydrous solvents were purchased from Sigma-Aldrich or Acros Organics in Sure-Seal^{TM} bottles for use as reaction solvents. All other solvents were reagent grade and used as received. Petroleum ether refers to the fraction that boils in the range 40-60 °C. Commercially available starting materials were used without purification.

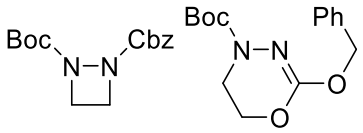
TLC was performed on pre-coated aluminium-backed plates (Merck Silicagel 60 F254), visualised by UV 254 nm then stained with phosphomolybdic acid (PMA) dip. Flash column chromatography was performed using Aldrich 40-63 µm Silica Gel.

Nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX (300 or 400 MHz) or AV (500 MHz, 600 MHz) spectrometers. Chemicals shifts (δ) are reported in parts per million (ppm) relative to the solvent residual peaks ($CDCl_3$ δ_H: 7.26 ppm, δ_C: 77.16 ppm; DMSO-d_6 δ_H: 2.50 ppm, δ_C: 39.52 ppm). Coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), or some combination of these.

Low-resolution mass spectra were recorded on an Agilent Technologies 6130 Quadrupole LC-MS instrument. High-resolution mass spectra were recorded using a Bruker MaXis Impact. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer and are given in cm^{-1}. Melting points were recorded with a Gallenkamp MPD350 apparatus and are reported as observed. Optical rotations were measured using an AA-1000 polarimeter and reported as observed.



2-Benzyl 1-(*tert*-butyl) 1-(2-iodoethyl)hydrazine-1,2-dicarboxylate (197) 196[84] (7.90 g, 25.0 mmol, 1.0 equiv), triphenylphosphine (7.88 g, 30.0 mmol, 1.2 equiv), imidazole (2.55 g, 37.5 mmol, 1.5 equiv.) and iodine (7.62 g, 30.0 mmol, 1.2 equiv) were combined in THF (50 mL) to give a purple solution which was stirred for 1 h. Saturated sodium sulphite solution (50 mL) was then added which gave a pale yellow solution that was stirred for 10 min. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL), then the combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography on silica gel (8:1 petroleum ether:ethyl acetate) gave **197** as a dark yellow oil (7.21 g, 17.3 mmol, 69%); R_f 0.14 (12% EtOAc in petroleum ether); IR (film) 3290, 2980, 1704, 1434, 1149; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 7.38 (5H, m, Ar-H), 5.20 (2H, s, CH_2Ph), 3.86 (2H, br m, CH_2N), 3.32 (2H, br m, CH_2I), 1.45 (9H, br s, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ*C* 152.8 (C=O), 133.8 (Ar-C), 126.9 (Ar-CH), 126.9 (Ar-CH), 66.2 (CH_2), 51.2 (CH_2), 50.4 (CH_2), 26.4 (CH_3), 1 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{15}H_{21}IN_2O_4$ $(M+Na)^+$: 443.0438; found: 443.0442.



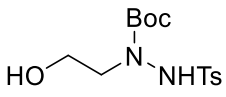
1-Benzyl 2-(*tert*-butyl) 1,2-diazetidine-1,2-dicarboxylate (198) and *tert*-butyl 2-(benzyloxy)-5,6-dihydro-4*H*-1,3,4-oxadiazine-4-carboxylate (199) 197 (1.00 g, 2.38 mmol, 1.0 equiv.) and Cs_2CO_3 (1.55 g, 4.76 mmol, 2.0 equiv.) were combined in acetonitrile (80 mL) and stirred for 24 h, at which point the reaction was shown to be complete by TLC. The crude mixture was passed through a plug of silica and celite using ethyl acetate as an eluent. The resulting liquid was concentrated *in vacuo* to give a yellow oil (0.68 g, 98% yield, 50:50 ratio of the two products determined by ^{1}H NMR). The two products were separated by column chromatography on silica gel (diethyl ether), which gave the 2 desired products, **198** (224 mg, 0.76 mmol, 29%); R_f 0.88 (diethyl ether); M.p. 88.2-89.7 °C; IR (film) 2974, 2925, 1742, 1713, 1439,

1379, 1285, 1118 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 7.38 (5H, m, Ph, Ar-H), 5.23 (2H, s, CH_2Ph), 4.26 (2H, m, NCH_2), 4.20 (2H, m, NCH_2), 1.48 (9H, s, $C(CH_3)_3$); ^{13}C NMR (125 MHz, CD_3CN) δ*C* 161.2 (C=O), 160.3 (C=O), 136.9 (Ar-C), 129.0 (Ar-CH), 128.7 (Ar-CH), 128.4 (Ar-CH), 81.9 (C), 67.9 (CH_2), 50.0 (CH_2), 49.9 (CH_2), 27.8 (CH_3); HRMS (ESI^+) calculated for $C_{15}H_{20}N_2O_4$ $(M+Na)^+$: 315.1318; found: 315.1315.

Single crystals of **198** were grown from dichloromethane/petroleum ether (1:9 ratio). A suitable crystal was selected and mounted on a glass fibre with Fromblin oil and placed on an Xcalibur Gemini diffractometer with a Ruby CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL refinement package using Least Squares minimisation.

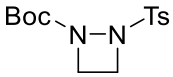
Crystal Data for **198** (*M* =292.33 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 12.0143(2) Å, *b* = 10.60779(18) Å, *c* = 12.1452(3) Å, *β* = 96.0212(15)°, *V* = 1539.31(5) $Å^3$, *Z* = 4, *T* = 150(2) K, μ(CuKα) = 0.760 mm^{-1}, *Dcalc* = 1.261 g/cm^3, 32897 reflections measured (7.398° ≤ 2Θ ≤ 161.944°), 3284 unique (R_{int} = 0.0413, R_{sigma} = 0.0166) which were used in all calculations. The final R_1 was 0.0402 (I > 2σ(I)) and wR_2 was 0.1109 (all data).

199 (326 mg, 1.11 mmol, 47%); R_f 0.84 (diethyl ether); M.p. 103.5-105.1 °C; IR (film) 2998, 2930, 1688, 1654, 1428, 1296; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 7.40 (5H, m, Ar-H), 5.20 (2H, s, CH_2Ph), 4.37 (2H, t, *J* 4.7, NCH_2), 3.79 (2H, t, *J* 4.8, NCH_2), 1.57 (9H, s, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ*C* 135.6 (Ar-C), 128.7 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 81.1 (C), 69.7 (CH_2), 65.4 (CH_2), 28.4 (CH_3), C=O not seen; HRMS (ESI^+) calculated for $C_{15}H_{20}N_2O_4$ $(M+Na)^+$: 315.1315; found: 315.1315.



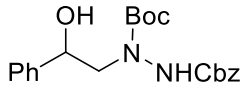
***tert*-Butyl 1-(2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (201) 200**[84] (1.15 g, 6.5 mmol, 1.0 equiv.), THF (10 mL), and pyridine (3.25 mL, 39 mmol, 6.0 equiv.)

were stirred and cooled with an ice bath. *p*-toluenesulfonylchloride (1.25 g, 6.5 mmol, 1.0 equiv.) was added portion wise over 5 min and the solution was stirred for a further 10 min. The ice bath was then removed and the resulting pale yellow solution was stirred for 3 h. 1 M HCl (10 mL), water (10 mL) and DCM (10 mL) were added and the layers were separated. The aqueous was washed with DCM (3 x 10 mL) and then the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a pale yellow solid. This was further purified by recrystallisation from hot toluene (50 mL) to give **201** as a white solid (1.38 g, 4.6 mmol, 71%); R_f 0.34 (30% EtOAc in petroleum ether); M.p. 123.3-124.2 °C; IR (film) 3385, 3120, 2923, 2875, 1674, 1400, 1337; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 7.80 (2H, d, *J* 8.2, Ar-H), 7.32 (2H, d, *J* 8.2, Ar-H), 3.98 (2H, t, *J* 8.0, NCH_2), 3.83 (2H, t, *J* 8.0, C*H*$_2$OH), 2.41 (3H, s, CH_3), 1.40 (9H, s, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ*C* 145.2 (C=O), 130.0 (Ar-CH), 128.8 (Ar-CH), 82.9 (C), 60.0 (CH_2) 54.0 (CH_2), 27.9 (CH_3), 21.7 (CH_3), 2 Ar-C not seen; HRMS (ESI$^+$) calculated for $C_{14}H_{22}N_2O_5S$ $(M+Na)^+$: 353.1142; found: 353.1149.

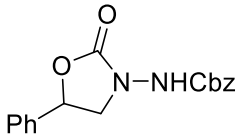


***tert*-Butyl 2-tosyl-1,2-diazetidine-1-carboxylate (202)** **201** (0.75 g, 2.30 mmol, 1.0 equiv.), triphenylphosphine (1.52 g, 5.80 mmol, 2.5 equiv.), and THF (20 mL) were stirred and cooled over an ice bath. Diethylazadicarboxylate (0.91 mL, 5.80 mmol, 2.5 equiv.) was added dropwise and the resulting pale yellow solution was warmed to rt and stirred for 24 h. The solution was then concentrated *in vacuo* to give a yellow oil, which was purified by column chromatography on silica gel (3:1 petroleum ether:ethyl acetate) to give **202** as a white crystalline solid (0.59 g, 1.91 mmol, 83%); M.p. 109-110 °C; IR (film) 2979, 2928, 1712, 1597, 1330, 1305, 1087; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 7.80 (2H d, *J* 8.2, Ar-CH), 7.32 (2H, d, *J* 8.1, Ar-CH), 3.98 (2H, t, *J* 8.0, NCH_2), 3.83 (2H, t, *J* 8.0, NCH_2), 2.41 (3H, s, CH_3), 1.40 (9H, s, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ*C* 159.1 (C=O), 145.2 (Ar-C), 130.1 (Ar-CH), 130.0 (Ar-C), 129.6 (Ar-CH), 82.9 (Ar-C), 48.9 (CH_2), 47.6 (CH_2), 27.9 (CH_3),

21.7 (CH_3); HRMS (ES^+) calculated for $C_{14}H_{20}N_2O_4S$ $(M+Na)^+$: 335.1036; found: 335.1033.



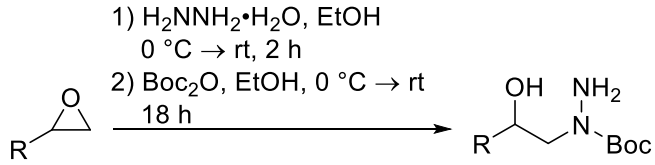
(*Rac*)-2-Benzyl 1-(*tert*-butyl) 1-(2-hydroxy-2-phenylethyl)hydrazine-1,2-dicarboxylate (207) Sodium hydroxide (170 mg, 4.24 mmol, 1.0 equiv.) was dissolved in dichloromethane (10 mL) and water (10 mL), then **(*Rac*)-206** (1.07 g, 4.24 mmol, 1.0 equiv.) was added. Benzyl chloroformate (0.61 mL, 4.24 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added dropwise to give a cloudy white solution, which was stirred for 22 h. The layers were then separated and the organic was washed with water (20 mL) and 1 M HCl (20 mL), then dried over Na_2SO_4 and concentrated *in vacuo* to give **207** as a white crystalline solid (1.15 g, 2.98 mmol, 70%), which was essentially pure, however, a small sample was recrystallized from hot toluene for analysis. M.p. 141.3-142.5 °C; IR (film) 3321, 3197, 3029, 2979, 1700, 1223, 1010; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 7.36 (10H, m, Ar-H), 6.66 (1H, br s, NH), 5.13 (2H, m, CH_2Ph), 4.91 (1H, m, C*H*OH), 3.54 (2H, m, NCH_2), 1.37 (9H, br s, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ*C* 155.0 (C=O), 140.9 (Ar-C), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 127.6 (Ar-CH), 126.0 (Ar-CH), 125.8 (Ar-CH), 74.0 (C), 71.3 (CH), 68.3 (CH_2), 29.7 (CH_2) 28.1 (CH_3), 1 C=O and 1 Ar-C not seen; HRMS (ES^+) calculated for $C_{21}H_{26}N_2O_5$ $(M+Na)^+$: 409.1734; found: 409.1726.



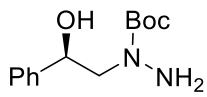
(*Rac*)-Benzyl (2-oxo-5-phenyloxazolidin-3-yl)carbamate (208) (*Rac*)-**207** (1.00 g, 2.71 mmol, 1.0 equiv) was dissolved in THF (20 mL) and stirred. Triphenylphosphine (0.85 g, 3.26 mmol, 1.2 equiv), imidazole (0.28 g, 4.05 mmol, 1.5 equiv) and iodine (0.83 g, 3.26 mmol, 1.0 equiv) were added and the resulting purple solution was stirred for 1 h. Saturated sodium sulfite solution (20 mL) was added, which gave a colourless solution and the mixture was stirred for a further 10 min. The layers were separated, and the

aqueous phase was extracted with ethyl acetate (3 x 20 mL), then the combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a pale yellow oil. Purification by column chromatography on silica gel (1:1 petroleum ether:ethyl acetate) gave **208** (0.43 g, 1.36 mmol, 42%) as a white crystalline solid. M.p. 128-129 °C; IR (film) 3227, 1724, 1454; ^{1}H NMR (500 MHz, *d6*-DMSO) δ*H* 9.90 (1H, br s, NH) 7.42 (10H, m, Ar-H), 5.69 (1H, t, *J* 7.1, CHPh), 5.16 (2H, s, CH_2Ph), 4.11 (1H, t, *J* 8.0, NC*H*H), 3.63 (1H, t, *J* 8.0, NCH*H*); ^{13}C NMR (125 MHz, *d6*-DMSO) δ*C* 157.1 (C=O), 155.6 (C=O), 138.7 (Ar-C), 136.5 (Ar-C), 129.5 (Ar-CH), 129.3 (Ar-CH), 129.0 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH), 126.9 (Ar-CH), 74.0 (CH_2), 67.0 (CH), 53.0 (CH_2); HRMS (ES^+) calculated for $C_{17}H_{16}N_2O_4$ $(M+Na)^+$: 335.1005; found: 335.1002.

General procedure 1: Ring opening and Boc protection of epoxides

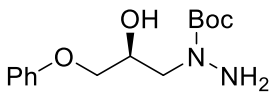


The epoxide (1.0 equiv) was added dropwise to a solution of hydrazine monohydrate (10.0 equiv) and anhydrous EtOH (0.1 M), that had been cooled to 0 °C using an ice bath. The reaction mixture was stirred at 0 °C for 2 h then concentrated *in vacuo*. Anhydrous EtOH (0.1 M) was then added and the solution was cooled to 0 °C using an ice bath. Di-*tert*-butyl dicarbonate (1.0 equiv) in EtOH (20 mL) was added *via* syring pump over 2 h. The solution was then left to warm to rt adn stirred for 16 h. The crude product was concentrated *in vacuo* then purified by column chromatography (5% MeOH/ CH_2Cl_2 or 19% EtOAc/petroleum ether with 1% Et_3N) to give the hydrazine.

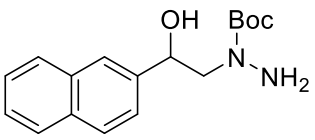


(*R*)-*tert*-Butyl 1-(2-hydroxy-2-phenylethyl)hydrazine-1-carboxylate (206) Following general procedure 1, Ethanol (2 mL), hydrazine monohydrate (4.70 mL, 100 mmol, 10.0 equiv), (*R*)-2-phenyloxirane (1.14 mL, 20 mmol, 1.0 equiv) then Ethanol (15 mL) and di-*tert*-butyl dicarbonate (4.37 g, 20.0 mmol, 1.0 equiv) gave **206** (3.83

g, 15.0 mmol, 75%) as a white crystalline solid. N.B. this was further purified by recrystallisation from toluene to give an analytical sample M.p. 101-103 °C; $[\alpha]^{27}_D$ = - 1.29 (*c* 0.40, $CHCl_3$); IR (fim) 3411, 3330, 2975, 1660, 1347, 1164; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 7.36 (5H, m, Ar-H), 5.04 (1H, m, C*H*OH), 4.28 (1H, s, OH), 4.24 (2H, s, NH_2), 3.77 (1H, dd, *J* 14.4, 7.9, NC*H*H), 3.62 (1H, dd, *J* 14.4, 7.9, CH*H*), 1.44 (9H, s, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ*C* 156.8 (C=O), 141.9 (Ar-C), 128.4 (Ar-CH), 127.6 (Ar-CH), 125.8 (Ar-CH), 81.2(C), 76.1 (CH), 74.1 (CH_2), 28.3 (CH_3); HRMS (ES^+) calculated for $C_{13}H_{20}N_2O_3$ $(M+Na)^+$: 275.1366; found: 275.1365. The racemic compound was synthesised using the same methodology with (*Rac*)-2-phenyloxirane.

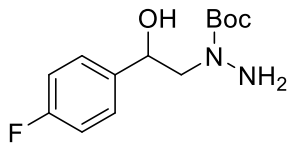


***tert*-Butyl-(*R*)-1-(2-hydroxy-3-phenoxypropyl)hydrazine-1-carboxylate (214)** Following general procedure 1, hydrazine monohydrate (4.86 mL, 100 mmol, 10.0 equiv), ethanol (5 mL), (*R*)-glycidyl phenyl ether (1.35 mL, 10 mmol, 1.0 equiv) then di-*tert*-butyldicarbonate (2.18 g, 10 mmol) and ethanol (6 mL) gave **214** as a colourless oil (1.66 g, 59%); R_f 0.21 (5% MeOH/dichloromethane); IR (film) 3332, 2976, 1689, 1495, 1242, 1163, 995; $[\alpha]^{32}_D$ + 10.9 (*c* 0.09, $CHCl_3$); δH (500 MHz, $CDCl_3$) 7.30 (2H, t, *J* 5.0, Ar-H), 6.97 (1H, t, *J* 5.0, Ar-H), 6.93 (2H, d, *J* 8.0, Ar-H), 4.34-4.19 (1H, m, C*H*OH), 4.03-3.98 (2H, m, NCH_2), 3.94 – 3.57 (5H, m, NH_2, OH and OCH_2), 1.48 (9H, s, CH_3).); δC (126 MHz, $CDCl_3$) 158.5 (C=O), 156.9 (Ar-C), 129.5 (Ar-CH), 121.1 (Ar-CH), 114.5 (Ar-CH), 81.3 (C), 69.9 (CH), 55.1 (CH_2), 52.3 (CH_2), 28.3 (CH_3); HRMS (ES^+) *calculated* for $C_{14}H_{22}N_2O_4Na$ $(M+Na)^+$: 305.1472; found: 305.1473.

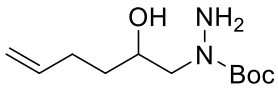


***tert*-Butyl (*Rac*)-1-(2-hydroxy-2-(naphthalen-2-yl)ethyl)hydrazine-1-carboxylate (215)** Following general procedure 1**,** hydrazine monohydrate (4.50 mL, 93 mmol, 10.0 equiv.), ethanol (5 mL),

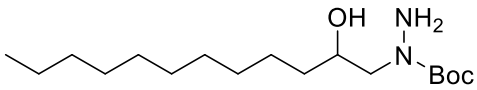
naphthyl oxirane (1.59 g, 9.3 mmol, 1.0 equiv) in ethanol (30 mL) then ethanol (10 mL) and di-*tert*-butyldicarbonate (2.23 g, 10.2 mmol) in ethanol (6 mL) gave **215** as a white solid (1.82 g, 65%). R_f 0.62 (10% MeOH/dichloromethane); M.p. 89-92 °C; IR (film) 3399, 2972, 1664, 1309, 1161, 1128; δH (500 MHz, $CDCl_3$) 7.90-7.84 (4H, m, Ar-H), 7.59-7.40 (3H, m, Ar-H), 5.19 (1H dd, *J* 7.6, 2.2, C*H*OH), 3.86 (1H, dd, *J* 14.5, 2.5 Hz NC*H*H), 3.70 (1H, dd, *J* 16.0, 6.0, NCH*H*), 1.42 (9H, s, CH_3); δC (126 MHz, $CDCl_3$) 156.8 (C=O), 139.3 (Ar-C), 133.3 (Ar-C), 133.0 (Ar-C), 128.1 (Ar-CH), 127.9 (Ar-CH), 127.7 (Ar-CH), 126.1 (Ar-CH), 125.9 (Ar-CH), 124.7 (Ar-CH), 124.0 (Ar-CH), 81.3 (C), 74.1 (CH), 56.7 (CH_2), 28.2 (CH_3); HRMS (ES^+) *calculated* for $C_{17}H_{22}N_2O_3Na$ $(M+Na)^+$: 325.1523; found: 325.1523.



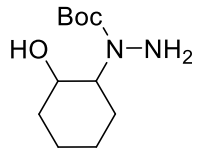
***tert*-Butyl (*Rac*)-1-(2-(4-fluorophenyl)-2-hydroxyethyl)hydrazine-1-carboxylate (216)** Following general procedure 1, hydrazine monohydrate (3.41 mL, 70 mmol, 10.0 equiv), ethanol (5 mL), 4-fluorophenyloxirane (960 mg, 7 mmol, 1.0 equiv) in ethanol (5 mL) then ethanol (6 mL) and di-*tert*-butyldicarbonate (1.68 g, 7.7 mmol, 1.1 equiv) in ethanol (6 mL) gave **216** as a white solid (1.66 g, 5.7 mmol, 59%). R_f 0.35 (5% MeOH/dichloromethane); M.p. 131-134 °C; IR (film) 3378, 2978, 1740, 1666, 1508, 1303, 1164, 1090; δH (500 MHz, $CDCl_3$) 7.37 (2H, dd, *J* 7.8, 5.8, Ar-H), 7.07 (2H, t, *J* 8.6, Ar-H), 5.00 (1H, dd, *J* 7.7, 2.1, C*H*OH), 3.73 (1H, dd, *J* 14.4, 2.6 Hz, NC*H*H), 3.57 (1H, dd, *J* 14.4, 7.8, NCH*H*), 1.48 (9H, s, CH_3). δC (126 MHz, $CDCl_3$) 162.3 (d, *J* 239.4, Ar-CF), 156.7 (C=O), 137.6 (d, *J* = 3.1 Hz, Ar-C), 127.5 (d, *J* 8.1 Hz, Ar-CH), 115.3 (d, *J* 21.4, Ar-CH), 81.4 (C), 73.5 (CH), 56.6 (CH_2), 28.3 (CH_3); δF (376 MHz, $CDCl_3$) -115.2 (Ar-F); HRMS (ES^+) *calculated* for $C_{13}H_{19}N_2O_3FNa$ $(M+Na)^+$: 293.1272; found: 293.1273.



***tert*-Butyl-(*Rac*)-1-(2-hydroxyhex-5-en-1-yl)hydrazine-1-carboxylate (216a)** Following general procedure 1, hydrazine monohydrate (1.45 mL, 30 mmol, 10.0 equiv), ethanol (30 mL) and (*Rac*)-1,2-epoxy-5-hexene (0.34 mL, 3.0 mmol, 1.0 equiv) then ethanol (30 mL) and di-*tert*-butyldicarbonate (0.66 g, 3.0 mmol, 1.0 equiv) in ethanol (20 mL) gave **216a** as a colourless oil (427 mg, 63%); R_f 0.15 (19% EtOAc/petroleum ether with 1% Et_3N); IR (film) 3367, 3198, 2978, 2932, 1706, 1451, 1231, 1003; δH (400 MHz, $CDCl_3$) 5.50 (1H, ddt, *J* 16.9, 10.2, 6.6, H_2C=C*H*), 5.01 (1H, dd, *J* 17.1, 1.4, *H*HC=CH), 4.94 (1H, d, *J* 10.0, H*H*C=CH), 4.14 (2H, s, NH_2), 3.90-3.78 (2H, m, C*H*OH and OH), 3.50 (1H, dd, *J* 14.3, 2.3, C*H*HNBoc), 3.32 (1H, dd, *J* 14.2, 7.6, CH*H*NBoc), 2.25-2.05 (2H, m, CH_2CHOH), 1.57-1.45 (2H, m, H_2C=CHCH_2), 1.43 (9H, s, CH_3); δC (100 MHz, $CDCl_3$) 156.7 (C=O), 138.3 (H_2C=*C*H), 114.8 (H_2*C*=CH), 81.1 (C), 70.9 (CH), 54.8 (CH_2), 33.8 (CH_2), 29.7 (CH_2), 28.3 (CH_3); HRMS (ES^+) calculated for $C_{11}H_{22}N_2O_3$ $(M+Na)^+$: 253.1523; found: 253.1518.

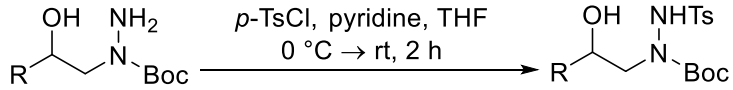


***tert*-Butyl-(*Rac*)-1-(2-hydroxydodecyl)hydrazine-1-carboxylate (216b)** Following general procedure 1, hydrazine monohydrate (1.45 mL, 30 mmol, 10.0 equiv), ethanol (30 mL) and (*Rac*)-1,2-epoxydodecane (0.65 mL, 3 mmol, 1.0 equiv) then ethanol (30 mL) and di-*tert*-butyldicarbonate (0.66 g, 3 mmol, 1.0 equiv) in ethanol (10 mL) gave **216b** as a colourless oil (270 g, 30%); R_f 0.51 (5% MeOH/CH_2Cl_2); IR (film) 3372, 3202, 2978, 1706, 1495, 1289, 1161; δH (400 MHz, $CDCl_3$) 3.88-3.72 (1H, m, C*H*OH), 3.66-3.49 (1H, m, C*H*HNBoc), 3.40-3.25 (1H, m, CH*H*NBoc), 1.52-1.40 (11H, m, $(CH_3)_3$, CH_2CHOH), 1.32-1.20 (16H, m, $(CH_2)_8$), 0.88 (3H, t, *J* 6.5, CH_3); δC (100 MHz, $CDCl_3$) 156.9 (C=O), 81.0 (C), 71.4 (CH), 55.0 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 28.3 (CH_3), 25.5 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (ES^+) calculated for $C_{17}H_{36}N_2O_3$ $(M+Na)^+$: 339.2618; found: 339.2610.

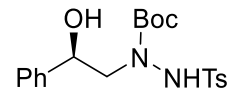


***tert*-Butyl-(*Rac*)-1-(2-hydroxycyclohexyl)hydrazine-1-carboxylate (216c)** Following general procedure 1, hydrazine monohydrate (0.26 mL, 8.8 mmol, 10.0 equiv), ethanol (2 mL) and cyclohexene oxide (112 µL, 0.88 mmol, 1.0 equiv) then ethanol (10 mL) and di-*tert*-butyldicarbonate (193 mg, 0.88 mmol, 1.0 equiv) in ethanol (10 mL) gave **216c** as a colourless oil (150 mg, 0.65 mmol, 74%); R_f 0.45 (5% MeOH/CH_2Cl_2); IR (film) 3368, 3198, 2978, 1705, 1364, 1232, 1157, 995; δH (400 MHz, $CDCl_3$) 6.43 (2H, s, NH_2), 3.26-3.15 (1H, m, C*H*OH), 2.45-2.33 (1H, m, CHNBoc), 1.98-1.71 (2H, m, C*H*$_2$CHOH), 1.65-1.58 (2H, m, C*H*$_2$CHNBoc), 1.39 (9H, s, CH_3), 1.21-1.10 (4H, m, CH_2CH_2); δC (100 MHz, $CDCl_3$) 158.1 (C=O), 80.8 (C), 71.2 (CH), 65.8 (CH), 33.4 (CH_2), 29.2 (CH_2), 28.4 (CH_3), 24.8 (CH_2), 24.5 (CH_2); HRMS (ES^+) calculated for $C_{11}H_{22}N_2O_3$ $(M+Na)^+$: 253.1523; found: 253.1520.

General procedure 2: Tosyl protection

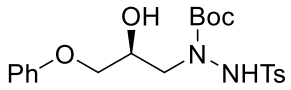


The hydrazine (1.0 equiv), in THF (0.1 M) and *para*-toluenesulfonylchloride (1.1 equiv) were combined and stirred over an ice bath. Pyridine (5.0 equiv) was then added dropwise over 1 minute. After 2 h a mix of 1 M HCl was added, then the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (20-40% EtOAc/petroleum ether) to give the tosylated product.

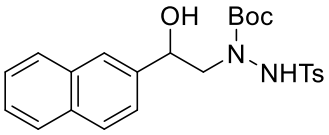


(*R*)-*tert*-Butyl 1-(2-hydroxy-2-phenylethyl)-2-tosylhydrazine-1-carboxylate (211) Following general procedure 2, **206** (200 mg, 0.79 mmol, 1.0 equiv.), pyridine (6 mL) and *para*-toluenesulfonylchloride (316 mg, 1.66 mmol, 2.1 equiv.) gave **211** as a white solid (280 mg, 0.67 mmol, 85%); R_f = 0.21 (25% EtOAc in petroleum ether); M.p. 138-139 °C; $[\alpha]_D^{28}$ = - 4.81 (*c* 0.12, $CHCl_3$); IR (film)

3456, 3128, 2975, 1709, 1089; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 7.82 (2H, d, *J* 8.2, Ar-H), 7.36 (7H, m, Ar-H), 5.17 (1H, dd, *J* 9.9, 3.6, CHPh), 3.86 (1H, br m, NC*H*H), 3.74 (1H, d, *J* 9.9, NCH*H*), 2.44 (3H, s, CH_3), 1.18 (9H, br s, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ*C* 144.6 (C=O), 141.4 (Ar-C), 132.2 (Ar-C), 132.1 (Ar-C) 130.0 (Ar-CH), 129.8 (Ar-CH), 128.6 (Ar-CH), 128.0 (Ar-CH), 126.0 (Ar-CH), 82.9 (C), 75.2 (CH), 58.8 (CH_2) 27.8 (CH_3), 21.6 (CH_3); HRMS (ES^+) calculated for $C_{20}H_{26}N_2O_5S$ $(M+Na)^+$: 429.1451; found: 429.1455.

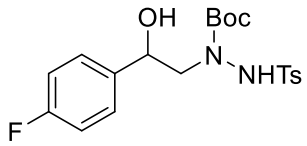


***tert*-Butyl-(*R*)-1-(2-hydroxy-3-phenoxypropyl)-2-tosylhydrazine-1-carboxylate (437)** Following generalprocedure 2, **214** (660 mg, 2.30 mmol, 1.0 equiv), THF (25 mL) and *para*-toluenesulfonylchloride (496 mg, 2.60 mmol, 1.1 equiv) gave **437** as a colourless oil (807 mg, 79%); R_f 0.28 (33% EtOAc/petroleuem ether); IR (film) 3247, 2979, 1704, 1598, 1242, 1089, 1040; $[\alpha]^{32}_D$ - 19.7 (*c* 0.23, $CHCl_3$); δH (500 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8.2, Ar-H), 7.41-7.29 (4H, m, Ar-H), 7.00 (1H, t, *J* 7.3, Ar-H), 6.93 (2H d, *J* 8.2, Ar-H), 4.45-4.37 (1H, m, C*H*OH), 4.24-3.69 (4H, m, OCH_2 and NCH_2), 2.46 (3H, s, CH_3), 1.27 (9H, s, CH_3); δC (126 MHz, $CDCl_3$) 158.4 (C=O), 144.7 (Ar-C), 129.6 (Ar-CH), 128.8 (Ar-CH), 121.3 (Ar-CH), 114.6 (Ar-CH), 114.5 (Ar-CH), 83.0 (C), 69.5 (CH_2), 69.0 (CH_2), 27.6 (CH_3), 21.6 (CH_3), 1 CH and 2 Ar-C not seen; HRMS (ES^+) *calculated* for $C_{21}H_{28}N_2O_6SNa$ $(M+Na)^+$: 459.1560; found: 459.1563.

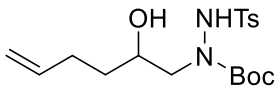


***tert*-Butyl (*Rac*)-1-(2-hydroxy-2-(naphthalen-2-yl)ethyl)-2-tosylhydrazine-1-carboxylate (438)** Following general procedure 2, **215** (700 mg, 2.3 mmol, 1.0 equiv), THF (50 mL) and *para*-toluenesulfonylchloride (477 mg, 2.5 mmol, 1.1 equiv) gave **438** as a white solid (166 mg, 16%). R_f 0.47 (33% EtOAc/petroleum ether); M.p. 145-147 °C; IR (film) 3471, 2927, 1708, 1672, 1383, 1155, 1125; δH (500 MHz, MeOD) 7.94-7.71 (6H, m, Ar-H), 7.60-7.25

(5H, m, Ar-H), 5.15 (1H, s, C*H*OH), 4.23-3.48 (2H, m, NCH_2), 2.41 (3H, s, CH_3), 1.16 (minor rotamer) and 0.77 (9H, s, CH_3); δC (126 MHz, MeOD) 144.1 (Ar-C), 139.7 (Ar-C), 133.4 (Ar-C), 133.2 (Ar-C), 129.2 (Ar-CH), 128.3 (Ar-CH), 127.7 (Ar-CH), 127.5 (Ar-CH), 127.2 (Ar-CH), 125.7 (Ar-CH), 125.5 (Ar-CH), 124.0 (Ar-CH), 81.4 (C), 72.7 (CH), 63.9 (CH_2), 26.3 (CH_3), 20.1 (CH_3), 1 C=O, 1 Ar-C and 1 Ar-CH not seen; HRMS (ES^+) *calculated* for $C_{24}H_{28}N_2O_5SNa$ $(M+Na)^+$: 479.1611; found: 479.1615.

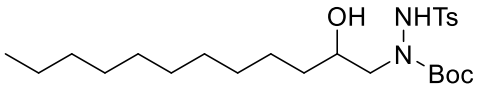


***tert*-Butyl (*Rac*)-1-(2-(4-fluorophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (439)** Following general procedure 2, **216** (660 mg, 2.3 mmol, 1.0 equiv), THF (25 mL) and *para*-toluenesulfonylchloride (496 mg, 2.6 mmol, 1.1 equiv) gave **439** as a white solid (807 mg, 1.80 mmol, 79%). R_f 0.29 (33% EtOAc/petroleum ether); M.p.157-158 °C; IR (film) 3455, 3126, 2930, 1709, 1510, 1367, 1224; δH (500 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8.2, Ar-H), 7.40-7.32 (4H, m, Ar-H), 7.07 (2H, t, *J* 8.6, Ar-H), 5.16 (1H, dd, *J* 9.1, 3.4, C*H*OH), 3.75 (2H, m, NCH_2), 2.45 (3H, s, CH_3), 1.18 (9H, s, CH_3); δC (126 MHz, $CDCl_3$) 162.4 (d, *J* 252.0, Ar-CF), 144.7 (Ar-C), 137.1 (Ar-C), 129.6 (Ar-CH), 128.8 (Ar-CH), 127.7 (d, *J* 8.1, Ar-CH), 115.4 (d, *J* 21.4, Ar-CH). 83.1 (C), 73.8 (CH), 59.1 (CH_2), 27.6 (CH_3), 21.6 (CH_3), 1 C=O and 1 Ar-C not seen; δF (376 MHz, $CDCl_3$) -114.5 (Ar-F); HRMS (ES^+) *calculated* for $C_{20}H_{25}N_2O_5FSNa$ $(M+Na)^+$: 447.1360; found: 447.1358.

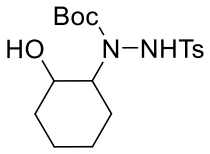


***tert*-Butyl-(*Rac*)-1-(2-hydroxyhex-5-en-1-yl)-2-tosylhydrazine-1-carboxylate (439a)** Following general procedure 2, **216a** (258 mg, 1.12 mmol, 1.0 equiv), THF (11 mL), *para*-toluenesulfonylchloride (235 mg, 1.23 mmol, 1.1 equiv) and pyridine (0.45 mL, 5.6 mmol, 5.0 equiv) gave **439a** as a colourless oil (261 mg, 61%); R_f 0.22 (20% EtOAc/petroleum ether); IR (film) 3393, 3179, 2971, 2937, 1707, 1317, 1242, 977; δH (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* 8.1, Ar-H), 7.25 (2H, d, *J* 8.5, Ar-H),

5.77 (1H, ddt, *J* 16.9, 10.2, 6.6, H_2C=C*H*), 4.99 (1H, dd, *J* 17.1, 1.0, *H*HC=CH), 4.92 (1H, d, *J* 10.1, H*H*C=CH), 4.01-3.91 (1H, br m, C*H*OH), 3.62-3.43 (2H, br m, CH_2NBoc), 2.36 (3H, s, CH_3), 2.19 (1H, td, *J* 14.2, 7.0, C*H*HCHOH), 2.08 (1H, td, *J* 14.8, 7.6, CH*H*CHOH), 1.46 (2 H, dd, *J* 14.5, 7.2, H_2C=CHCH_2), 1.11 (9H, s, $(CH_3)_3$); δC (100 MHz, $CDCl_3$) 155.4 (C=O), 144.5 (Ar-C), 138.1 (H_2C=*C*H), 129.5 (Ar-CH), 128.7 (Ar-CH), 115.0 (H_2C=CH), 82.7 (C), 69.0 (CH – seen on HSQC), 57.2 (CH_2 – seen on HSQC), 33.8 (CH_2), 29.7 (CH_2), 27.6 (CH_3), 21.5 (CH_3), 1 Ar-C not seen; HRMS (ES^+) calculated for $C_{18}H_{28}N_2SO_5$ $(M+Na)^+$: 407.1611; found: 407.1618.



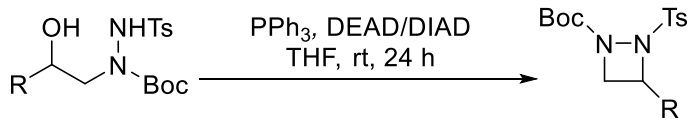
***tert*-Butyl-(*Rac*)-1-(2-hydroxydodecyl)-2-tosylhydrazine-1-carboxylate (439b)** Following general procedure 2 **216b** (270 mg, 0.85 mmol, 1.0 equiv), THF (8 mL), *para*-toluenesulfonylchloride (179 mg, 0.94 mmol, 1.1 equiv) and pyridine (0.34 mL, 4.3 mmol, 5.0 equiv) gave **439b** as a colourless oil (162 mg, 40%); R_f 0.33 (30% EtOAc/petroleuem ether); IR (film) 3341, 2982, 1727, 1694, 1403, 1242, 1129; δH (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* 7.8, Ar-H), 7.31 (2H, d, J 7.9, Ar-H), 4.05-3.93 (1H, m, C*H*OH), 3.70-3.52 (2H, m, CH_2NBoc), 2.42 (3H, s, CH_3), 1.45-1.39 (2H, m, CH_2CHOH), 1.32-1.20 (17H, m, $(CH_3)_3$, $(CH_2)_4$), 1.20-1.12 (8H, m, $(CH_2)_4$), 0.89 (3H, t, *J* 6.5, CH_3); δC (100 MHz, $CDCl_3$) 155.4 (C=O), 144.4 (Ar-C), 137.0 (Ar-C), 129.5 (Ar-CH), 128.7 (Ar-CH), 82.6 (C), 71.6 (CH), 46.6 (CH_2), 34.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 27.6 (CH_3), 25.5 (CH_2), 22.7 (CH_2), 21.5 (CH_3), 14.1 (CH_3); HRMS (ES^+) calculated for $C_{24}H_{42}N_2O_5S$ $(M+Na)^+$: 493.2707; found: 493.2707.



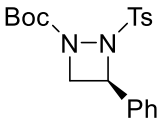
***tert*-Butyl-(*Rac*)-1-(2-hydroxycyclohexyl)-2-tosylhydrazine-1-carboxylate (439c) 216c** (108 mg, 0.47 mmol, 1.0 equiv), THF (5 mL), *para*-toluenesulfonylchloride (99 mg, 0.52 mmol, 1.1 equiv) and pyridine (189 µL, 2.4 mmol, 5.0 equiv) gave **439c** as a white solid (127 mg, 0.33 mmol, 70%); R_f 0.29

(20% EtOAc/petroleum ether); M.p. 173-174 °C; IR (film) 3167, 2941, 1727, 1699, 1495, 1184; δH (400 MHz, $CDCl_3$) 8.17 (2H, d, *J* 8.1, Ar-H), 7.64 (2H, d, *J* 8.1, Ar-H), 4.89 (1H, d, *J* 1.8, C*H*OH), 4.27-4.18 (1H, m, CHNBoc), 3.75-3.65 (1H, m, C*H*HCHOH), 3.60-3.52 (1H, m, C*H*HCHOH), 2.76 (3H, s, CH_3), 2.47-2.38 (2H, m, C*H*$_2$CHNBoc), 2.13-2.04 (4H, m, CH_2CH_2), 1.66 (9H, s, CH_3); δC (100 MHz, $CDCl_3$) 156.0 (C=O), 144.3 (Ar-C), 135.1 (Ar-C), 129.4 (Ar-CH), 128.5 (Ar-CH), 82.4 (C), 69.2 (CH), 65.1 (CH), 32.6 (CH_2), 27.8 (CH_3), 24.8 (CH_2), 24.0 (CH_2), 21.5 (CH_3); HRMS (ES^+) calculated for $C_{18}H_{28}N_2O_5S$ $(M+Na)^+$: 407.1611; found: 407.1616.

General procedure 3: Mitsunobu reaction



The hydrazine (1.0 equiv), THF (0.01 M), triphenylphosphine (2.5 equiv) and diethylazodicarboxylate or diisopropylazodicarboxylate (2.5 equiv) were combined and stirred at rt. After 24 h it was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (20-40% EtOAc/petroleum ether) to give the cyclised product.

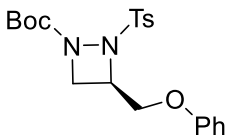


***tert*-Butyl (*S*)-3-phenyl-2-tosyl-1,2-diazetidine-1-carboxylate (212)** Following general procedure 3, **211** (48 mg, 0.12 mmol, 1.0 equiv), triphenylphosphine (79 mg, 0.30 mmol, 2.5 equiv), THF (12 mL, 0.01 M) and diethylazadicarboxylate (48 µL, 0.30 mmol, 2.5 equiv) gave **212** as a white crystalline solid (31 mg, 80 µmol, 67%); M.p. 166-167 °C; $[\alpha]_D^{28}$ = + 7.62 (*c* 0.21, $CHCl_3$); Enantiomeric excess (99% *ee*) was determined by HPLC analysis (25 °C). [Chiralcel OD column 2-propanol/hexane = 2/98; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 15.8 min; t_R 19.0 min. IR (film) 2980, 2932, 1733, 1395, 1358; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 7.93 (2H d, *J* 8.2, Ar-CH), 7.37 (7H, m, Ar-CH), 5.06 (1H, dd, *J* 8.7, 5.9, CHPh), 4.21 (1H, t, *J* 8.7, NC*H*H), 3.96 (1H, dd, *J* 8.5, 5.9,

NCH*H*), 2.51 (3H, s, CH_3), 1.45 (9H, s, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ*C* 159.3 (C=O), 145.2 (Ar-C), 137.6 (Ar-C), 130.8 (Ar-CH), 130.1 (Ar-CH), 130.0 (Ar-C), 129.6 (Ar-CH), 128.9 (Ar-CH), 126.4 (Ar-CH), 82.9 (C), 61.3 (CH), 56.3 (CH_2), 28.0 (CH_3), 21.8 (CH_3); HRMS (ES^+) calculated for $C_{20}H_{24}N_2O_4S$ $(M+Na)^+$: 411.1349; found: 411.1352.

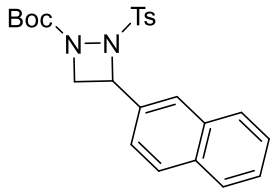
Single crystals of **212** were grown from dichloromethane/hexane. A suitable crystal was selected and mounted on a glass fibre with Fromblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a duel source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150 K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL refinement package using Least Squares minimisation.

Crystal Data for **212** (*M* =388.47 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 6.21070(10) Å, *b* = 16.8428(4) Å, *c* = 18.7007(4) Å, *V* = 1956.20(7) $Å^3$, *Z* = 4, *T* = 150(2) K, μ(CuKα) = 1.707 mm^{-1}, *Dcalc* = 1.319 g/cm^3, 20599 reflections measured ($7.064° \leq 2\Theta \leq 147.372°$), 3913 unique ($R_{int}$ = 0.0663, R_{sigma} = 0.0392) which were used in all calculations. The final R_1 was 0.0326 ($I > 2\sigma(I)$) and wR_2 was 0.0818 (all data).

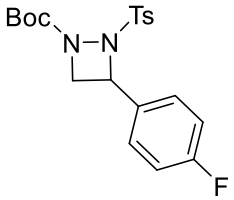


***tert*-Butyl (*R*)-3-(phenoxymethyl)-2-tosyl-1,2-diazetidine-1-carboxylate (218)** Following general procedure 3, **437** (337 mg, 0.77 mmol, 1.0 equiv), triphenylphosphine (507 mg, 1.90 mmol, 2.5 equiv), THF (77 mL, 0.01M) and diethylazadicarboxylate (303 μL, 1.90 mmol, 2.5 equiv) gave **218** as a white crystalline solid (203 mg, 0.47 mmol, 62%); R_f 0.29 (15% EtOAc/petroleum ether); M.p.119-122 °C; IR (film) 2979, 1739, 1597, 1492, 1150, 1087; $[\alpha]^{32}_D$ – 7.7 (*c* 0.11, $CHCl_3$); Enantiomeric excess (98% *ee*) was determined by HPLC analysis (25 °C). [Chiralcel OD column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 20.5 min; t_R 23.0 min; δH (500 MHz, $CDCl_3$) 7.91 (2H, d, *J* 8.2, Ar-H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.31 (2H, t, *J*

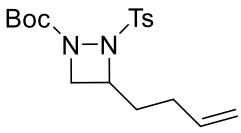
8.0, Ar-H), 7.01 (1H, t, *J* 7.3, Ar-H), 6.93 (2H, d, *J* 8.0, Ar-H), 4.41-4.27 (2H, m, NCH_2), 4.18-4.10 (2H, m, OCH_2), 3.93 (1H, t, *J* 8.4, NC*H*CH_2), 2.50 (3H, s, CH_3), 1.43 (s, 9H); δC (126 MHz, $CDCl_3$) 159.2 (C=O), 158.3 (Ar-C), 145.2 (Ar-C), 130.5 (Ar-C), 130.0 (Ar-CH), 129.7 (Ar-CH), 129.5 (Ar-CH), 121.5 (Ar-CH), 114.8 (Ar-CH), 82.7 (C), 67.7 (CH_2), 58.3 (CH), 51.3 (CH_2), 27.9 (CH_3), 21.7 (CH_3); HRMS (ES^+) *calculated* for $C_{21}H_{26}N_2O_5S$ $(M+Na)^+$: 444.1455; found: 444.1449.



***tert*-Butyl (*Rac*)-3-(naphthalen-2-yl)-2-tosyl-1,2-diazetidine-1-carboxylate (219)** Following general procedure 3, **438** (120 mg, 0.26 mmol, 1.0 equiv), triphenylphosphine (170 mg, 0.65 mmol, 2.5 equiv), THF (26 mL, 0.01 M) and diethylazadicarboxylate (102 µL, 0.65 mmol, 2.5 equiv) gave **219** as a white crystalline solid (35 mg, 80 µmol, 31%). R_f 0.47 (25% EtOAc/petroleum ether); M.p. 145-147 °C; IR (film) 2977, 1741, 1395, 1321, 1153; δH (400 MHz, d6-DMSO) 8.10-7.70 (5H, m, Ar-H), 7.72-7.40 (4H, m, Ar-H), 7.24-7.16 (2H, m, Ar-H), 7.01 (1H, t, *J* 7.3, Ar-H), 5.70-5.65 (minor rotamer) and 5.32-5.25 (1H, m, CHAr), 4.50-4.41 (minor rotamer) and 4.30-4.20 (1H, m, NC*H*H), 4.00-3.92 and 3.82-3.77 (minor rotamer, 1H, m, NCH*H*), 3.93 (1H, t, *J* 8.4, NC*H*CH_2), 2.48 and 2.45 (minor rotamer, 3H, s, CH_3), 1.42 and 1.29 (minor rotamer, 9H, s, CH_3); δC (100 MHz, d6-DMSO) 159.2 (C=O), 145.9, 145.5 (minor, Ar-C), 135.6, 134.7 (minor, Ar-C), 134.5 (minor), 133.7 (Ar-C), 133.3 (minor), 133.0 (Ar-C), 131.4 (minor), 130.3 (Ar-C), 130.6 (minor), 130.5 (Ar-CH), 130.2, 129.2 (minor, Ar-CH), 128.4 (Ar-CH), 128.2, 128.1 (minor, Ar-CH), 127.5, 127.4 (minor, Ar-CH), 127.2, 127.2 (minor, Ar-CH), 126.9 (minor), 126.2 (Ar-CH), 125.8 (minor), 124.5 (Ar-CH), 123.3 (Ar-CH), 82.7, 81.9 (minor, C), 62.1, 57.1 (minor, CH), 56.8 (CH_2), 28.0, 27.9 (minor, CH_3), 21.7, 21.6 (minor, CH_3); HRMS (ES^+) *calculated* for $C_{24}H_{26}N_2O_4S$ $(M+Na)^+$: 461.1505; found: 461.1498.

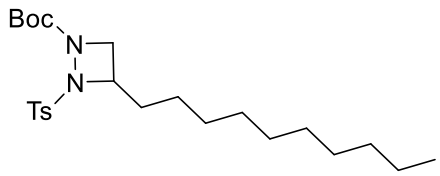


***tert*-Butyl (*Rac*)-3-(4-fluorophenyl)-2-tosyl-1,2-diazetidine-1-carboxylate (220)** Following general procedure 3, **439** (337 mg, 0.77 mmol, 1.0 equiv), triphenylphosphine (507 mg, 1.93 mmol, 2.5 equiv), THF (77 mL, 0.01 M) and diethylazadicarboxylate (303 µL, 1.93 mmol, 2.5 equiv) gave **220** as a white crystalline solid (118 mg, 36%). R_f 0.20 (25% EtOAc/pet ether); M.p. 153-156 °C; IR (film) 3493, 2965, 1710, 1326, 1168, 1043; δH (500 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8.1, Ar-H), 7.39-7.31 (4H, m, Ar-H), 7.06 (2H, t, *J* 8.6, Ar-H), 5.16 (1H, dd, *J* 9.0, 3.4, NCHAr), 3.95-3.63 (2H, m, CH_2), 2.44 (3H, s, CH_3), 1.18 (9H, s, CH_3); δC (126 MHz, $CDCl_3$) 162.4 (d, *J* 252.0, Ar-CF), 144.8 (Ar-C), 137.1 (d, *J* 2.7, Ar-C), 129.6 (Ar-CH), 128.8 (Ar-CH), 127.7 (d, *J* 8.1 Hz, Ar-CH), 115.4 (d, *J* 21.5, Ar-CH), 83.1 (C), 74.2 (CH), 58.9 (CH_2), 27.6 (CH_3), 21.6 (CH_3), 1 C=O and 1 Ar-C not seen; HRMS (ES^+) *calculated* for $C_{20}H_{23}N_2O_4FSNa$ $(M+Na)^+$: 429.1255; found: 429.1251.

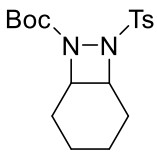


***tert*-Butyl-(*Rac*)-3-(but-3-en-1-yl)-2-tosyl-1,2-diazetidine-1-carboxylate (220a)** Following general procedure 3, **439a** (23 mg, 60 µmol, 1.0 equiv), THF (6 mL, 0.01 M), triphenylphosphine (39 mg, 0.15 mmol, 2.5 equiv) and diisopropylazodicarboxylate (30 µL, 0.15 mmol, 2.5 equiv) gave **220a** as a white solid (18 mg, 49 µmol, 82%); R_f 0.31 (15% EtOAc/petroleum ether); M.p. 84-86 °C; IR (film) 3336, 3242, 2958, 2848, 1710, 1437, 1174; δH (400 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.2, Ar-H), 7.35 (2H, d, *J* 8.1, Ar-H), 5.77 (1H, ddt, *J* 16.8, 10.2, 6.5, H_2C=C*H*), 5.05 (1H, dd, *J* 17.1, 1.3, *H*HC=CH), 4.99 (1H, d, *J* 10.2, H*H*C=CH), 3.97 (1H, dt, *J* 13.2, 6.6, C*H*OH), ^{1}H NMR (400 MHz, $CDCl_3$) 3.79 (1H, t, *J* 8.3, C*H*HNBoc), 3.61 (1H, dd, *J* 8.5, 5.5, CH*H*NBoc), 2.45 (3H, s, CH_3), 2.22-2.09 (2H, m, *J* 14.2, 7.0, CH_2CHNTs), 1.95 (1H, td, *J* 14.2, 7.0, H_2C=CHC*H*H), 1.83-1.75 (1H, m, H_2C=CHCH*H*), 1.41 (9H, s, $(CH_3)_3$); δC (100 MHz, $CDCl_3$) 159.2 (C=O), 145.0 (Ar-C), 136.9 (H_2C=*C*H), 130.8 (Ar-C), 129.9 (Ar-CH), 129.5 (Ar-CH), 115.7 (H_2*C*=CH), 82.6 (C), 59.7 (CH), 54.2 (CH_2),

33.8 (CH_2), 28.4 (CH_2), 27.9 (CH_3), 21.7 (CH_3); HRMS (ES^+) calculated for $C_{18}H_{26}N_2O_4$ $(M+Na)^+$: 389.1505; found: 389.1514.

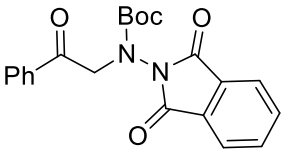


***tert*-Butyl-(*Rac*)-3-decyl-2-tosyl-1,2-diazetidine-1-carboxylate (220b)** Following general procedure 3, **439b** (34 mg, 72 µmol, 1.0 equiv), THF (8 mL, 0.01 M), triphenylphosphine (47 mg, 0.18 mmol, 2.5 equiv) and diisopropylazodicarboxylate (36 µL, 0.18 mmol, 2.5 equiv) gave **220b** as a colourless oil (30 mg, 67 µmol, 93%); R_f 0.17 (10% EtOAc/petroleuem ether); IR (film) 3382, 2956, 1747, 1721, 1459, 1495, 1213, 1186; δH (500 MHz, $CDCl_3$) major rotamer reported 7.85 (2H, d, *J* 8.2, Ar-H), 7.36 (2H, d, *J* 8.1, Ar-H), 4.02 – 3.93 (1H, m, CHNTs), 3.81 (1H, t, *J* 8.3, C*H*HNBoc), 3.63 (1H dd, *J* 8.5, 5.4, CH*H*NBoc), 2.46 (3H, s, CH_3), 1.80 (1H, dt, *J* 9.9, 7.2, C*H*HCHNTs), 1.75 – 1.65 (1H, m, CH*H*CHNTs), 1.42 (9H, s, $(CH_3)_3$), 1.26 (16H, s, $(CH_2)_8$), 0.88 (3H, t, *J* 7.5, CH_3); δC (126 MHz, $CDCl_3$) 159.3 (C=O), 144.9 (Ar-C), 130.9 (Ar-C), 130.0 (Ar-CH), 129.5 (Ar-CH), 128. (Ar-CH), 82.6 (C), 60.4 (CH), 54.2 (CH_2), 34.6 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 28.0 (CH_3), 24.1 (CH_2), 22.7 (CH_2), 21.7 (CH_3), 14.1 (CH_3). HRMS (ES^+) calculated for $C_{24}H_{40}N_2O_4S$ $(M+Na)^+$: 475.2588; found: 475.2592.

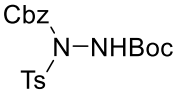


***tert*-Butyl-(*Rac*)-8-tosyl-7,8-diazabicyclo[4.2.0]octane-7-carboxylate (220c)** Following general procdure 3, **439c** (38 mg, 0.10 mmol, 1.0 equiv), THF (10 mL), triphenylphosphine (66 mg, 0.25 mmol, 2.5 equiv) and diisopropylazodicarboxylate (50 µL, 0.25 mmol, 2.5 equiv) gave **220c** as a white solid (32 mg, 87 µmol 87%); R_f 0.42 (30% EtOAc/petroleum ether); M.p. 138-139 °C; IR (film) 3368, 2955, 1729, 1152, 1118; δH (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.2, Ar-H), 7.34 (2H, d, *J* 8.1, Ar-H), 4.13-4.03 (2H, m, CHNBoc, CHNTs), 2.44 (3H, s, CH_3), 2.10-2.01 (2H, m, C*H*$_2$CHNTs), 1.96-1.86 (2H, m, C*H*$_2$CHNBoc), 1.65-1.43 (4H, m, CH_2CH_2),

1.44 (9H, s, CH_3); δC (100 MHz, $CDCl_3$) 156.7 (C=O), 144.8 (Ar-C), 130.6 (Ar-C), 129.9 (Ar-CH), 129.5 (Ar-CH), 82.1 (C), 59.6 (CH), 58.2 (CH), 27.3 (CH_3), 24.2 (CH_2), 21.7 (CH_3), 16.4 (CH_2), 16.2 (CH_2), 1 CH_2 not seen; HRMS (ES^+) calculated for $C_{18}H_{26}N_2O_4$ $(M+Na)^+$: 389.1505; found: 389.1505.



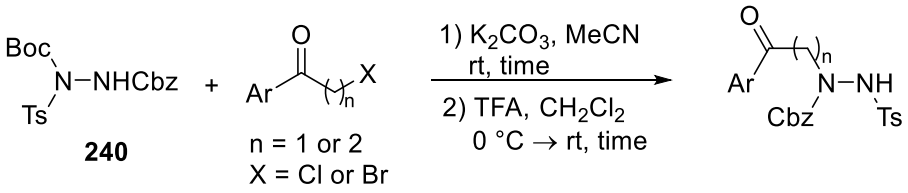
***tert*-Butyl (1,3-dioxoisoindolin-2-yl) (2-oxo-2-phenylethyl)carbamate (237)** 2-Bromoacetophenone (209 mg, 1.05 mmol), acetonitrile (10 mL), *tert*-butyl (1,3-dioxoisoindolin-2-yl)carbamate[94] (**236**) (170 mg, 1 mmol) and potassium carbonate (145 mg, 1.05 mmol) were combined and stirred at rt. After 3 h, the reaction was quenched with water (10 mL), extracted with dichloromethane (3 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give **237** as a white solid (270 mg, 0.71 mmol, 71%). M.p. 85-88 °C; IR (film) 3066, 3007, 2897, 2919, 1795, 1724, 1701, 1281; δH ^{1}H NMR (400 MHz, $CDCl_3$) 8.02 (2H, d, *J* 7.4, Ar-CH), 7.95-7.87 (3H, m, Ar-CH), 7.84-7.75 (3H, m, Ar-CH), 7.61 (1H, t, *J* 7.2, Ar-CH), 7.50 (1H, q, *J* 7.9, Ar-CH), 5.19 and 5.08 (minor rotamer) (2H, s, $COCH_2$), 1.51-1.35 (9H, m, CH_3); ^{13}C NMR δC (125 MHz, $CDCl_3$) 191.1 (CO), 189.4 (CO), 163.2 (CO), 162.8 (CO), 151.3 and 150.9 (minor rotamer) (Ar-C), 133.1 (minor rotamer) and 133.1 (Ar-C), 132.8 and 132.7 (minor rotamer) (Ar-CH), 128.1 (minor rotamer) and 128.0 (Ar-C), 126.9 (minor rotamer) and 126.8 (Ar-CH), 126.3 and 126.3 (minor rotamer) (Ar-CH), 122.0 and 122.0 (minor rotamer) (Ar-CH), 83.5 (minor rotamer) and 83.1 (C), 54.4 (minor rotamer) and 52.0 (CH_2), 26.1 (minor rotamer) and 25.9 (CH_3), 1 Ar-CH not seen; MS (ES^+) *m/z* = 403 ($[M+Na]^+$, 100); HRMS (ES^+) *calculated* for $C_{21}H_{20}N_2O_5Na$ $(M+Na)^+$: 403.1264; found: 403.1266.



1-Benzyl 2-(*tert*-butyl) 1-tosylhydrazine-1,2-dicarboxylate (281). *tert*-Butyl 2-tosylhydrazine-1-carboxylate (**227**)[137] (3.22 g, 11.3 mmol, 1.0 equiv), triethylamine (1.65 mL, 11.8 mmol, 1.05 equiv), 4-dimethylaminopyridine (138 mg, 1.1 mmol, 0.1 equiv) and

dichloromethane (20 mL) were stirred at 0 °C. Then benzyl chloroformate (1.69 mL, 11.8 mol, 1.05 equiv) in dichloromethane (20 mL) was added via syringe pump over 1 h. The reaction mixture was then quenched with sodium hydrogen carbonate (20 mL), extracted with dichloromethane (3 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. The crude product was purified by column chromatography (15% EtOAc/pet ether) to give **281** (4.35 g, 10.4 mmol, 92%) as a colourless oil. R_f = 0.12 (15% EtOAc in petroleum ether); IR (film) 3336, 2981, 1736, 1365, 1155 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.92 (2H, d, *J* 8.0, Ar-*H*), 7.36-7.25 (7H, m, Ar-*H*), 6.95 and 6.63 (minor rotamer) (1H, s, NH), 5.28-5.13 (2H, m, C*H*$_2$Ph), 2.44 (3H, s, C*H*$_3$) 1.49 (9H, s, C(CH_3)$_3$); δ*C* (125 MHz; $CDCl_3$) 153.5 (C=O), 151.5 (C=O), 145.3 (Ar-C), 131.7 (Ar-C), 134.2 (Ar-C), 129.6 (Ar-CH), 129.2 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 82.8 (C), 69.6 (CH_2), 28.0 (CH_3), 21.7 (CH_3); HRMS (ESI^+) calculated for $C_{20}H_{24}N_2NaO_6S$ $[M+Na]^+$ 443.1247; found 443.1245.

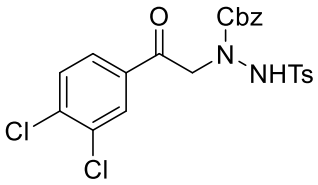
General Procedure 4: Synthesis of keto hydrazines using triply protected hydrazine 240



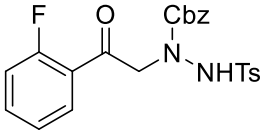
Scheme 6.1 General procedure for keto hydrazine synthesis using **240**.

To a solution of hydrazine **240**[95] (1.0 equiv) in anhydrous CH_3CN (0.1 M) was added halide (1.1 equiv) followed by potassium carbonate (1.1 equiv). The reaction mixture was stirred at rt until completion of the reaction (6-24 h). Water (10 mL) was then added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (15-40% EtOAc/ pet ether) to give the tetrasubstituted hydrazide. To this compound (1.0 equiv) in dichloromethane (0.1 M) was added

trifluroacetic acid (10 equiv) at 0 °C. After 2 h, the reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (15-40% EtOAc/ pet ether) to give the following compounds.

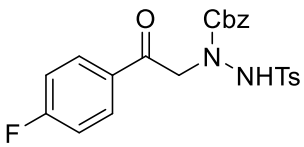


Benzyl 1-(2-(3,4-dichlorophenyl)-2-oxoethyl)-2-tosylhydrazine-1-carboxylate (249). Following general procedure 4, hydrazide **240** (204 mg, 0.76 mmol, 1.0 equiv), 2-bromo-3`,4`-dichloroacetophenone (212 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (8.0 mL, 0.1 M), then trifluoroacetic acid (586 µL, 7.60 mmol, 10 equiv) and dichloromethane (8.0 mL, 0.1 M) gave **249** (157 mg, 0.31 mmol, 41%) as a white solid. R_f = 0.22 (15% EtOAc in petroleum ether); M.p. 174-177 °C. IR (film) 3257, 2928, 1710, 1421, 1183 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.97 (1H, d, *J* 8.9, Ar-*H*), 7.81-7.67 (3H, m, Ar-*H*), 7.58 (1H, d, *J* 8.2, Ar-*H*) 7.37-7.01 (7H, m, Ar-*H*), 5.07-4.87 (4H, m, NCH_2 and CH_2Ph), 2.43 and 2.39 (minor rotamer) (3H, s, CH_3); δ*C* (125 MHz, $CDCl_3$) 191.8 (C=O, major rotamer), 191.4 (C=O, minor rotamer), 156.7 (C=O), 144.7 (Ar-C), 138.9 (Ar-C) 133.8 (Ar-C), 133.7 (Ar-C), 131.1 (Ar-CH), 130.0 (Ar-CH), 129.6 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 126.9 (Ar-CH), 68.9 (CH_2), 58.8 (CH_2, major rotamer), 58.0 (CH_2, minor rotamer), 21.8 (CH_3), 2 Ar-C not seen; HRMS (ESI^+) calculated for $C_{23}H_{20}{}^{35}Cl_2N_2O_5S$ $[M+Na]^+$ 529.0362; found 529.0357.

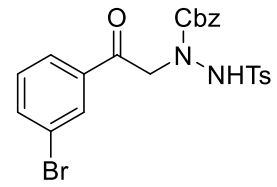


Benzyl 1-(2-(2-fluorophenyl)-2-oxoethyl)-2-tosylhydrazine-1-carboxylate (250). Following general procedure 4, hydrazide **240** (300 mg, 0.72 mmol, 1.0 equiv), 2-bromo-2`-fluoroacetophenone (171 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (8.0 mL, 0.1 M), then trifluoroacetic acid (555 µL, 7.20 mmol, 10.0 equiv) and dichloromethane (8.0 mL, 0.1 M) gave **250** (204 mg, 0.45 mmol, 62%) as a white

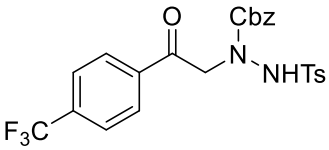
solid. R_f = 0.21 (15% EtOAc in petroleum ether); M.p. 122-123 °C; IR (film) 3211, 2966, 1721, 1693, 1609, 1499, 1255, 1200 cm^{-1}; δ*H* (600 MHz; D6-DMSO at 100 °C) 9.97 (1H, s, NH), 7.80 (1H, t, *J* 7.5 Ar-*H*), 7.73-7.67 (3H, m, Ar-*H*), 7.38-7.27 (7H, m, Ar-*H*), 7.21-7.14 (2H, m, Ar-H), 4.84 (2H, s, CH_2Ph), 4.81 (2H, s, NCH_2) 2.36 (3H, s, CH_3); δ*C* (150 MHz, D6-DMSO at 100 °C) 144.0 (Ar-C), 136.1 (d, *J* 9.0, Ar-CH) 130.6 (Ar-CH), 129.7 (Ar-CH), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.2 (Ar-CH), 127.8 (Ar-CH), 125.4 (Ar-CH), 117.2 (d, *J* 24 Ar-CH), 68.0 (CH_2), 61.7 (CH_2), 21.4 (CH_3), 2 C=O, 4 Ar-C not seen; δ*F* (376 MHz, D6-DMSO) -108.8 (C-F); HRMS (ESI^+) calculated for $C_{23}H_{21}FN_2O_5S$ $[M+Na]^+$ 479.1047; found 479.1048.



Benzyl 1-(2-(4-fluorophenyl)-2-oxoethyl)-2-tosylhydrazine-1-carboxylate 252 Following general procedure 4, hydrazide **240** (300 mg, 0.72 mmol, 1.0 equiv), 2-bromo-4`-fluoroacetophenone (171 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (8.0 mL, 0.1 M), then trifluoroacetic acid (555 µL, 7.20 mmol, 10.0 equiv) and dichloromethane (8.0 mL, 0.1 M) gave **252** (141 mg, 0.31 mmol, 43%) as a white solid. R_f = 0.20 (15% EtOAc in petroleum ether); M.p. 124-127 °C. IR (film) 3250, 2944, 1721, 1692, 1595, 1339, 1270 cm^{-1}; δH (500 MHz; $CDCl_3$) 8.03 (1H, d, *J* 23.3 Ar-*H*), 7.86-7.68 (4H, m, Ar-*H*), 7.41-7.03 (7H, m, Ar-*H*), 5.10-4.87 (4H, m, NCH_2 and CH_2Ph), 2.43 and 2.39 (minor rotamer) (3H, s, CH_3).; δC (125 MHz, $CDCl_3$) 192.1 (C=O), 156.8 (C=O) 144.6 (Ar-C), 137.0 (Ar-CH) 136.7 (Ar-C, seen on HMBC), 135.5 (Ar-C), 129.5 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 126.5 (Ar-CH), 123.3 (Ar-C) 68.9 (CH_2), 58.9 (CH_2, major rotamer), 58.1 (CH_2, minor rotamer), 21.8 (CH_3), 3 Ar-C not seen; δF (282 MHz, $CDCl_3$) -102.8 (CF); HRMS (ESI^+) calculated for $C_{23}H_{21}FN_2O_5S$ $[M+Na]^+$ 479.1047; found 479.1052.

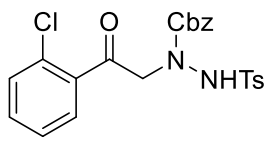


Benzyl 1-(2-(3-bromophenyl)-2-oxoethyl)-2-tosylhydrazine-1-carboxylate (253). Following general procedure 4, hydrazide **240** (300 mg, 0.72 mmol, 1.0 equiv), 2,3‘-bromoacetophenone (220 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (8.0 mL, 0.1 M), then trifluoroacetic acid (555 µL, 7.20 mmol, 10 equiv) and dichloromethane (8.0 mL, 0.1 M) gave **253** (201 mg, 0.39 mmol, 54%) as a white solid. R_f = 0.18 (15% EtOAc in petroleum ether); M.p. 131-133 °C. IR (film) 3230, 2964, 2919, 1719, 1682, 1494, 1343, 1215 cm^{-1}; δH (500 MHz; $CDCl_3$) 8.03 (1H, d, *J* 8.3, Ar-*H*), 7.86-7.68 (4H, m, Ar-*H*), 7.41-7.02 (8H, m, Ar-*H*), 5.09-4.85 (4H, m, NCH_2 and CH_2Ph), 2.43 and 2.39 (minor rotamer) (3H, s, CH_3); δC (125 MHz, $CDCl_3$) 192.1 (C=O), 156.8 (C=O), 144.6 (Ar-C), 137.0 (Ar-CH), 131.1 (Ar-CH), 130.5 (Ar-CH), 129.5 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.0 (Ar-CH), 126.5 (Ar-CH), 123.3 (Ar-C), 68.9 (CH_2), 58.9 (CH_2) and 58.1 (CH_2, minor rotamer), 21.8 (CH_3), 3 Ar-C not seen; HRMS (ESI^+) calculated for $C_{23}H_{21}{}^{79}BrN_2O_5S$ $[M+Na]^+$ 539.0247; found 539.0240.

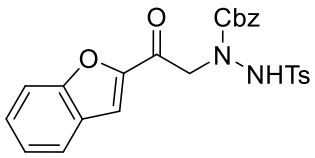


Benzyl 1-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-2-tosylhydrazine-1-carboxylate (254). Following general procedure 4, hydrazine **240** (300 mg, 0.72 mmol, 1.0 equiv), 2-bromo-4‘-(trifluoromethyl)acetophenone (211 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (8.0 mL, 0.1 M), then trifluoroacetic acid (555 µL, 7.20 mmol, 10 equiv) and dichloromethane (8.0 mL, 0.1 M) gave **254** (204 mg, 0.40 mmol, 56%) as a white solid. R_f = 0.19 (15% EtOAc in petroleum ether); M.p. 203-205 °C. IR (film) 3263, 2925, 1710, 1687, 1324, 830, 811 cm^{-1}; δH (500 MHz; $CDCl_3$) 8.05-7.97 (2H, m, Ar-*H*), 7.81-7.68 (4H, m, Ar-*H*), 7.36-7.03 (7H, m, Ar-*H*), 5.11-4.87 (4H, m, NCH_2 and CH_2Ph), 2.43 and 2.39 (minor rotamer) (3H, s, CH_3); δC (125 MHz, $CDCl_3$) 192.4 (C=O, seen on HMBC), 144.0 (Ar-C, seen on HMBC),

136.7 (Ar-C, seen on HMBC), 135.5 (Ar-C), 129.6 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 126.0 (Ar-CH), 68.9 (CH_2), 59.1 (CH_2) and 58.3 (CH_2, minor rotamer), 21.8 (CH_3), CF_3, 2 Ar-C and C=O not seen; δ*F* (376 MHz; $CDCl_3$) -63.3 (CF_3); HRMS (ESI^+) calculated for $C_{24}H_{21}F_3N_2O_5S$ $[M+Na]^+$ 529.1015; found 529.1016.

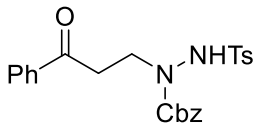


Benzyl 1-(2-(2-chlorophenyl)-2-oxoethyl)-2-tosylhydrazine-1-carboxylate (255). Following general procedure 4, hydrazide **240** (300 mg, 0.72 mmol, 1.0 equiv), 2-bromo-2`-chloroacetophenone (184 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (7.2 mL, 0.1 M), then trifluoroacetic acid (555 µL, 7.20 mmol, 10 equiv) and dichloromethane (7.2 mL, 0.1 M) gave **240** (191 mg, 0.40 mmol, 56%) as a white solid. R_f = 0.42 (25% EtOAc in petroleum ether); M.p. 89-93 °C; IR (film) 3195, 2941, 1728, 1704, 1417, 1382, 1219 cm^{-1}; δ*H* (500 MHz; d6-DMSO) 10.63 and 10.52 (minor rotamer) (1H, s, NH), 7.76-7.43 (5H, m, Ar-*H*), 7.36-7.10 (8H, m, Ar-*H*), 5.15-4.35 (4H, m, NCH_2 and CH_2Ph), 2.30 (3H, s, CH_3); δ*C* (125 MHz, d6-DMSO) 195.7 (C=O), 155.6 (C=O), 144.0 (Ar-C), 137.8 (Ar-C), 136.1 (Ar-C), 135.8 (Ar-C), 133.8 (Ar-CH), 131.2 (Ar-CH), 130.8 (Ar-C), 130.2 (Ar-CH), 129.8 (Ar-CH), 129.4 (Ar-CH), 128.7 (Ar-CH), 128.1 (Ar-CH), 127.8 (Ar-CH), 125.8 (Ar-CH), 67.8 (CH_2), 60.8 (CH_2), 21.6 (CH_3); HRMS (ESI^+) calculated for $C_{23}H_{21}{}^{35}ClN_2O_5S$ $[M+Na]^+$ 495.0752; found 495.0737.

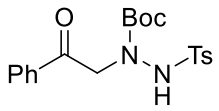


Benzyl 1-(2-(benzofuran-2-yl)-2-oxoethyl)-2-tosylhydrazine-1-carboxylate (258). Following general procedure 4, hydrazide **240** (300 mg, 0.72 mmol, 1.0 equiv), 2-bromo-1-(2,3-dihydrobenzofuran-2-yl)ethan-1-one (190 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (7.2 mL, 0.1 M), Deprotection of the Boc group was achieved using 1 M HCl in dioxane (4 mL)

instead of trifluoroacetic acid and dichloromethane to give **258** (189 mg, 0.40 mmol, 50%) as a white solid. R_f = 0.37 (25% EtOAc in petroleum ether); M.p. 126-128 °C. IR (film) 3274, 3201, 2953, 1721, 1681, 1391, 1235 cm^{-1}; δH (500 MHz; $CDCl_3$) 7.80 (1H, d, *J* 7.6, Ar-H), 7.73 (2H, d, *J* 7.6 Ar-H), 7.58 (2H, d, *J* 7.8, Ar-H), 7.52 (1H, t, *J* 7.8, Ar-H), 7.38-7.04 (8H, m, Ar-*H*),, 5.15-4.85 (4H, m, NC*H*$_2$ and C*H*$_2$Ph), 2.43 and 2.39 (minor rotamer) (3H, s, C*H*$_3$).; δC (125 MHz, $CDCl_3$) 184.8 (C=O), 155.8 (C=O), 150.5 (Ar-C) 144.6 (Ar-C), 135.1 (Ar-C), 133.8 (Ar-C), 129.5 (Ar-CH), 128.9 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH) 128.1 (Ar-CH), 128.0 (Ar-CH), 126.7 (Ar-C) 124.3 (Ar-CH) 123.5 (Ar-CH), 113.7 (Ar-CH), 112.5 (Ar-CH), 68.9 (CH_2), 58.7 and 58.0 (minor rotamer) (CH_2), 21.8 (CH_3), 1 Ar-C not seen; HRMS (ESI^+) calculated for $C_{25}H_{22}N_2O_6S$ $[M+Na]^+$ 501.1091; found 501.1092.

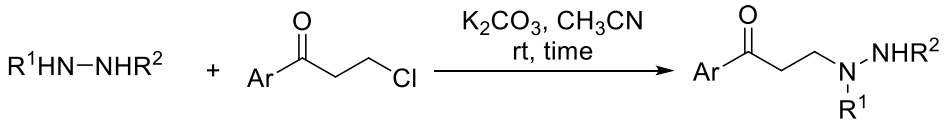


Benzyl 1-(3-oxo-3-phenylpropyl)-2-tosylhydrazine-1-carboxylate (287). Following general procedure 4, hydrazide **240** (300 mg, 0.72 mmol, 1.0 equiv), 3-chloropropiophenone (133 mg, 0.79 mmol, 1.1 equiv), potassium carbonate (109 mg, 0.79 mmol, 1.1 equiv) and acetonitrile (7.2 mL, 0.1 M), then trifluoroacetic acid (555 µL, 7.20 mmol, 10 equiv) and dichloromethane (7.2 mL, 0.1 M) gave **287** (293 mg, 0.65 mmol, 90%) as a white solid. R_f = 0.20 (15% EtOAc in petroleum ether); M.p. 122-123 °C; IR (film) 3231, 3034, 1702, 1666, 1380, 1307, 1184 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.95 (2H, d, *J* 7.8 Ar-H), 7.75 (2H, d, *J* 8.0, Ar-H), 7.60 (1H, t, *J* 7.3, Ar-H), 7.49 (2H, t, *J* 7.6, Ar-H), 7.33 (3H, d, *J* 4.9, Ar-H), 7.22 (2H, d, *J* 8.0, Ar-H), 7.15 (2H, s, Ar-H), 4.91 (2H, br s, CO_2CH_2), 4.08 (2H, br s, NCH_2), 3.40 (2H, br s, $COCH_2$), 2.42 (3H, s, Ar-CH_3); δ*C* (125 MHz, $CDCl_3$) 198.3 (C=O, seen on HMBC), 144.5 (Ar-C), 136.4 (Ar-C), 135.2 (Ar-C), 133.5 (Ar-CH), 129.6 (Ar-CH), 128.7 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.1 (Ar-CH), 128.1 (Ar-CH), 68.5 (CH_2), 46.8 (CH_2), 35.9 (CH_2), 21.7 (CH_3), 1 C=O, 1 Ar-H and 1 Ar-C not seen; HRMS (ESI^+) calculated for $C_{24}H_{24}N_2O_5S$ $[M+Na]^+$ 475.1298; found 475.1302.



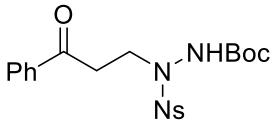
***tert*-Butyl 1-(2-oxo-2-phenylethyl)-2-tosylhydrazine-1-carboxylate (283).** Hydrazine **280** (310 mg, 0.74 mmol, 1.0 equiv), 2-bromoacetophenone (161 mg, 0.81 mol, 1.1 equiv), potassium carbonate (112 mg 0.81 mmol, 1.1 equiv) and acetonitrile (8.0 mL, 0.1 M) were stirred at room temperature for 24 h. The solution was then quenched with water (10 mL), extracted with dichloromethane (3 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. The product was purified by column chromatography (10% EtOAc in petroleum ether) to give a white solid. This was stirred under an atmosphere of hydrogen with 3 wt% palladium on charcoal (30 mg) and ethyl acetate (3.0 mL). The reaction was carefully monitored by TLC, as over-reduction to (*rac*)-**211** was seen to occur after Cbz removal. Generally, the reaction was complete in approximately 2 h. The crude reaction mixture was then filtered through a plug of Celite and concentrated *in vacuo* to give a colourless oil, which was purified by column chromatography (25% EtOAc in petroleum ether) to give **283** (153 mg, 0.38 mmol, 51%) as a white solid. R_f = 0.52 (25% EtOAc in petroleum ether); M.p. 148-150 °C; IR (film) 3219, 2981, 1710, 1695, 1329, 1156 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.93 (2H, d, *J* 7.4, Ar-*H*), 7.85 (2H, d, *J* 8.2, Ar-H), 7.64 (1H, q, *J* 8.0, Ar-H), 7.55-7.49 (2H, m, Ar-H), 7.41-7.30 (2H, m, Ar-*H*), 7.21 and 7.00 (minor rotamer) (1H, s, NH), 5.01 (2H, s, CH_2N), 2.50-2.42 (3H, m, CH_3), 1.20 and 1.15 (minor rotamer) (9H, s, C$(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 193.9 (minor rotamer) and 193.6 (C=O), 155.6 and 154.7 (minor rotamer, C=O), 144.5 (minor rotamer) and 144.4 (Ar-C), 134.5 (Ar-C), 134.0 (Ar-CH), 133.6 (Ar-C), 134.2 (Ar-CH), 133.9 (Ar-C), 129.7 (minor rotamer) and 129.3 (Ar-CH), 128.9 and 128.7 (minor rotamer, Ar-CH), 128.8 and 128.6 minor rotamer, Ar-CH), 128.0 (minor rotamer) and 127.9 (Ar-CH), 83.1 (minor rotamer) and 82.8 (C), 58.9, and 58.1 (minor rotamer, CH_2), 27.6 and 27.5 (minor rotamer, CH_3), 21.6 (CH_3); HRMS (ESI^+) calculated for $C_{20}H_{24}N_2NaO_5S$ $[M+Na]^+$ 427.1298; found 427.1296.

General procedure 5: Synthesis of keto hydrazines using protected hydrazines

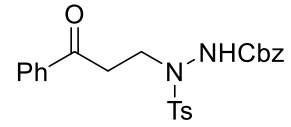


Scheme 6.2 General procedure for the synthesis of keto hydrazines.

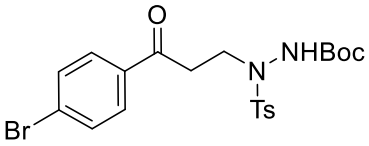
To a solution of protected hydrazine (1.0 equiv) in acetonitrile (0.1 M) was added the organic halide (1.0 equiv) followed by potassium carbonate (1.1 equiv). The reaction mixture was stirred at rt until completion of the reaction (6-24 h, monitored by TLC). Water (10 mL) was then added and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (30-40% EtOAc/ pet ether) to give the following compounds.



***tert*-Butyl 2-((4-nitrophenyl)sulfonyl)-2-(3-oxo-3-phenylpropyl)hydrazine-1-carboxylate (286).** Following general procedure 5, *tert*-butyl 2-((4-nitrophenyl)sulfonyl)hydrazine-1-carboxylate[138] (250 mg, 0.79 mmol, 1.0 equiv), acetonitrile (7.9 mL, 0.1 M), 3-chloropropiophenone (133 mg, 0.83 mmol, 1.05 equiv) and potassium carbonate (112 mg, 0.87 mmol, 1.1 equiv) yielded **286** as a white solid (249 mg, 0.56 mmol, 70%). R_f = 0.39 (25% EtOAc in petroleum ether); M.p; 157-159 °C; IR (film) 3316, 2984, 1735, 1679, 1526, 1317, 1208 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.80 (4H, t, *J* 9.1, Ar-CH), 7.61 (2H, d, *J* 8.3, Ar-CH), 7.32 (2H, d, *J* 7.8, Ar-CH), 6.36 (1H, br s, NH), 3.88 (2H, br s, $COCH_2$), 3.34 (2H, t, *J* 6.3, CH_2NNs), 1.27 (9H, br s, $C(CH_3)_3$); δ*C* (125 MHz, $CDCl_3$) 197.0 (C=O, seen on HMBC), 196.6 (C=O, seen on HMBC), 144.6 (Ar-C), 135.1 (Ar-C), 133.8 (Ar-C), 132.0 (Ar-CH), 129.7 (Ar-CH), 129.6 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH),. 81.8 (C), 46.2 (NCH_2), 37.3 (CH_2), 27.9 (CH_3), 1 C=O not seen; HRMS (ESI^+) calculated for $C_{21}H_{25}{}^{79}BrN_2O_5S$ $[M+Na]^+$ 519.0560; found 519.0564.

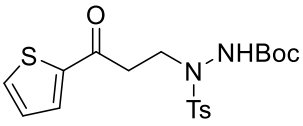


Benzyl 2-(3-oxo-3-phenylpropyl)-2-tosylhydrazine-1-carboxylate (**284**) Following general procedure 5, Benzyl 2-tosylhydrazine-1-carboxylate[95] (1.00 g, 3.10 mmol, 1.0 equiv), 3-choropropiophenone (0.52 g, 3.10 mmol, 1.0 equiv), potassium carbonate (0.45 g, 3.26 mmol, 1.05 equiv) and acetonitrile (31 mL, 0.1 M) to give **284** as a white solid (1.31 g, 2.90 mmol, 94%). R_f = 0.27 (25% EtOAc in petroleum ether). M.p. 144-146 °C. IR (film) 3310, 2941, 1744, 1680, 1328, 1164 cm^{-1}; δH (500 MHz; $CDCl_3$) 7.89 (2H, br s, Ar-CH), 7.75 (2H, d, *J* 8.0, Ar-CH), 7.57 (1H, t, *J* 7.4, Ar-CH), 7.44 (2H, t, *J* 7.3, Ar-CH), 7.34-7.29 (3H, m, Ar-CH), 7.27-7.15 (4H, m, Ar-CH), 6.57 (1H, br s, NH), 4.97 (2H, br s, $COOCH_2$), 3.87 (2H, br s, CH_2NTs), 3.37 (2H, br s, $COCH_2$), 2.41 (3H, s, Ar-CH_3); δC (125 MHz, $CDCl_3$) 144.7 (Ar-C), 136.3 (Ar-C), 135.4 (Ar-C), 133.5 (Ar-CH), 129.8, (Ar-CH), 128.7 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.4 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 67.8 (CH_2), 46.6 (CH_2), 37.0 (CH_2), 21.7 (Ar-CH_3), 2 C=O and 1 Ar-C not seen; HRMS (ESI^+) calculated for $C_{24}H_{24}N_2O_5S$ $[M+Na]^+$ 475.1298; found 475.1293.

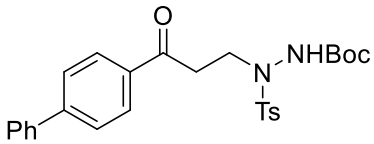


***tert*-Butyl 2-(3-(4-bromophenyl)-3-oxopropyl)-2-tosylhydrazine-1-carboxylate (288).** Following general procedure 5, *tert*-butyl 2-tosylhydrazine-1-carboxylate[138] (150 mg, 0.52 mmol, 1.0 equiv), acetonitrile (5.2 mL, 0.1 M), 4'-bromo-3-chloropropiophenone (129 mg, 0.52 mmol, 1.0 equiv) and potassium carbonate (75 mg, 0.55 mmol, 1.05 equiv) yielded **288** as a white solid (216 mg, 0.44 mmol, 85%). R_f = 0.29 (25% EtOAc in petroleum ether); M.p. 165-166 °C; IR (film) 3267, 2975, 2927, 1732, 1714, 1368, 1159 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.80 (4H, t, *J* 9.1, Ar-CH), 7.61 (2H, d, *J* 8.3, Ar-CH), 7.32 (2H, d, *J* 7.8, Ar-CH), 6.36 (1H, br s, NH), 3.88 (2H, br s, $COCH_2$), 3.34 (2H, t, *J* 6.3, CH_2NTs), 2.43 (3H, s, Ar-CH_3) 1.27 (9H, br s, $C(CH_3)_3$); δ*C* (125 MHz, $CDCl_3$) 197.0 (C=O, seen on HMBC), 196.6 (C=O, seen on HMBC), 144.6 (Ar-C), 135.1 (Ar-C), 133.8 (Ar-C), 132.0 (Ar-CH), 129.7 (Ar-CH), 129.6 (Ar-CH), 128.7 (Ar-C),

128.6 (Ar-CH), 81.8 (C), 46.2 (NCH_2), 37.3 (CH_2), 27.9 (CH_3), 21.6 (CH_3), 1 C=O not seen; HRMS (ESI^+) calculated for $C_{21}H_{25}{}^{79}BrN_2O_5S$ $[M+Na]^+$ 519.0560; found 519.0564.

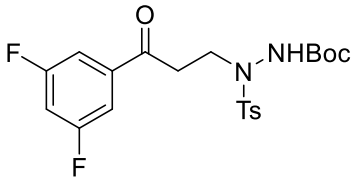


***tert*-Butyl 2-(3-oxo-3-(thiophen-2-yl)propyl)-2-tosylhydrazine-1-carboxylate (289).** Following general procedure 5, *tert*-butyl 2-tosylhydrazine-1-carboxylate[138] (200 mg, 0.70 mmol, 1.0 equiv), acetonitrile (7.0 mL, 0.1 M), 3-chloro-1-(thiophen-2-yl)propan-1-one (123 mg, 0.70 mmol, 1.0 equiv) and potassium carbonate (102 mg, 0.74 mmol, 1.05 equiv) yielded **289** as a pale yellow solid (222 mg, 0.52 mmol, 75%). R_f = 0.38 (25% EtOAc in petroleum ether); M.p. 39-40 °C; IR (film) 3320, 2978, 1718, 1654, 1347, 1237, 1152 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.80 (2H, t, *J* 8.2, Ar-H), 7.76 (2H, d, *J* 3.4, Ar-H), 7.68 (2H, d, *J* 4.8, Ar-H), 7.16 (1H, t, *J* 4.3, Ar-H), 6.35 (1H, br s, NH), 3.90 (2H, br s, $COCH_2$), 3.33 (2H, t, *J* 6.3, CH_2NTs), 2.45 (3H, s, CH_3) 1.28 (9H, br s, $C(CH_3)_3$); δ*C* (125 MHz, $CDCl_3$) 190.9 (C=O, seen on HMBC), 144.5 (Ar-C), 143.7 (Ar-C), 134.2 (Ar-CH), 132.6 (Ar-CH), 129.7 (Ar-CH), 129.6 (Ar-C, seen on HMBC), 128.6 (Ar-CH), 128.3 (Ar-CH), 81.7 (C), 46.3 (NCH_2), 38.0 (CH_2), 27.8 (CH_3), 21.6 (CH_3), Ar-CH and 1 C=O not seen; HRMS (ESI^+) calculated for $C_{19}H_{24}N_2O_5S_2$ $[M+Na]^+$ 447.1018; found 447.1021.



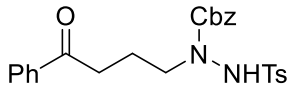
***tert*-Butyl 2-(3-([1,1'-biphenyl]-4-yl)-3-oxopropyl)-2-tosylhydrazine-1-carboxylate (290).** Following general procedure 5, *tert*-butyl 2-tosylhydrazine-1-carboxylate[138] (500 mg, 1.75 mmol, 1.00 equiv), acetonitrile (17.5 mL, 0.1 M), 1-([1,1'-biphenyl]-4-yl)-3-chloropropan-1-one[139] (470 mg, 1.92 mmol, 1.1 equiv) and potassium carbonate (265 mg, 1.92 mmol, 1.1 equiv) yielded **290** as a white solid (635 mg, 1.28 mmol, 73%). M.p. 156-157 °C; R_f = 0.34 (25% EtOAc in petroleum ether); IR (film) 3299, 2983, 2900, 1718, 1660, 1603, 1380, 1252 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 8.04 (2H, d, *J* 8.3, Ar-H), 7.82 (2H, d, *J* 8.2, Ar-H), 7.71 (2H, d, *J* 8.2, Ar-H), 7.65 (2H, d, *J* 7.4, Ar-H), 7.50 (2H, t, *J* 7.5, Ar-H), 7.43 (1H, t, *J* 7.3, Ar-H), 7.35 (2H, d, *J* 7.8, Ar-H), 3.93

(2H, br s, $COCH_2$), 3.43 (2H, t, *J* 6.1, CH_2NTs), 2.45 (3H, s, CH_3), 1.59 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz, $CDCl_3$) 197.6 (C=O, seen on HMBC), 146.1 (Ar-C), 144.5 (Ar-C), 139.8 (Ar-C), 135.1 (Ar-C), 129.7 (Ar-CH), 129.6 (Ar-C, seen on HMBC) 129.0 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.3 (Ar-CH), 127.3 (Ar-CH), 127.3 (Ar-CH), 81.5 (C, seen on HMBC), 46.4 (NCH_2), 41.4 (CH_2), 27.9 (CH_3), 21.6 (CH_3), 1 C=O not seen; HRMS (ESI^+) calculated for $C_{27}H_{30}N_2O_5S$ $[M+Na]^+$ 517.1768; found 517.1771.



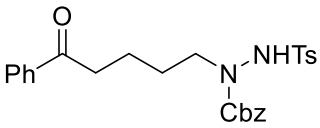
***tert*-Butyl 2-(3-(3,5-difluorophenyl)-3-oxopropyl)-2-tosylhydrazine-1-carboxylate (291).** Following general procedure 5, *tert*-butyl 2-tosylhydrazine-1-carboxylate[138] (350 mg, 1.22 mmol, 1.0 equiv), 3-chloro-1-(3,5-difluorophenyl)propan-1-one (250 mg, 1.22 mol, 1.1 equiv), potassium carbonate (185 mg, 1.34 mmol, 1.1 equiv) and acetonitrile (12 mL, 0.1 M) gave **291** (409 mg, 0.90 mmol, 74%) as a white solid. R_f = 0.29 (15% EtOAc in petroleum ether); M.p. 158-159 °C; IR (film) 3250, 2923, 1733, 1692, 1240, 1028 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.81 (2H, d, *J* 8.2, Ar-H), 7.46 (2H, d, *J* 5.6, Ar-H), 7.35 (2H, d, *J* 7.8, Ar-H), 7.05 (1H, t, J 8.2, Ar-H), 6.39 and 5.96 (minor rotamer) (1H, s, NH), 3.95-3.62 (2H, br m, C*H*$_2$N), 3.34 (2H, t, *J* 6.4, $COCH_2$), 2.45 (3H, s, C*H*$_3$), 1.30 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 164.2 (C=O), 163.1 (dd, *J* 251.4, 11.7, Ar-CF), 144.7 (Ar-C), 139.3 (Ar-C), 129.7 (Ar-CH), 128.6 (Ar-CH), 111.1 (dd, *J* 18.9, 6.3, Ar-CH), 108.7 (t, *J* 25.0, Ar-CH), 81.9 (C), 50.8 (CH_2), 46.0 (CH_2), 27.9 (CH_3), 21.6 (CH_3), 1 C=O and 1 Ar-C not seen; δ*F* (376 MHz; $CDCl_3$) -107.8 (Ar-CF); HRMS (ESI^+) calculated for $C_{21}H_{24}N_2NaO_5SF_2$ $[M+Na]^+$ 477.1266; found 477.1264.

Other Aryl Ketone Syntheses



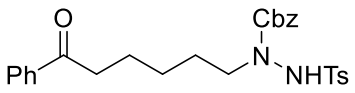
Benzyl 1-(4-oxo-4-phenylbutyl)-2-tosylhydrazine-1-carboxylate (318). Hydrazine **240**[95] (400 mg, 0.96 mmol, 1.0 equiv), 4-hydroxy-1-phenylbutan-1-one[101] 158 mg, 0.96 mmol, 1.0 equiv), triphenylphosphine (376 mg, 1.44 mmol, 1.5 equiv), diethyl

azodicarboxylate (224 µL, 1.44 mmol, 1.5 equiv) and tetrahydrofuran (10 mL, 0.1 M) were combined and stirred at room temperature for 24 h. The reaction mixture was then concentrated *in vacuo*. The crude product was purified by column chromatography (30% EtOAc/ pet ether) to give the tetrasubstituted hydrazide. To this hydrazine was added trifluoroacetic acid (735 µL, 9.60 mmol, 10.0 equiv) and dichloromethane (9.6 mL, 0.1 M), the solution was then stirred for 2 h. The resulting yellow solution was concentrated *in vacuo* to give a yellow oil, which was purified by column chromatography (25% EtOAc/pet ether) to yield **240** as a white solid (215 mg, 0.46 mmol, 48%). R_f = 0.26 (25% EtOAc in petroleum ether); M.p. 136-137 °C; IR (film) 3179, 3060, 2955, 1709, 1687, 1369, 1270 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.91 (2H, d, *J* 7.6 Ar-CH), 7.72 (2H, d, *J* 7.8, Ar-CH), 7.58 (1H, t, *J* 7.3, Ar-CH), 7.46 (2H, t, *J* 7.7, Ar-CH), 7.31 (3H, t, *J* 6.9, Ar-CH), 7.19 (2H, d, *J* 7.5, Ar-CH), 7.10-7.00 (3H, m, Ar-CH and NH), 4.78 (2H, br s, $COOCH_2$), 3.79 (2H, br s, CH_2NCbz), 3.01 (2H, br s, $COCH_2$), 2.41 (3H, s, Ar-CH_3), 2.15-2.08 (2H, m, $COCH_2CH_2$); δ*C* (125 MHz, $CDCl_3$) 199.2 (C=O, seen on HMBC), 144.4 (Ar-C), 136.7 (Ar-C), 135.2 (Ar-C), 133.2 (Ar-CH), 129.5 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 127.7 (Ar-C), 68.3 (CH_2), 50.6 (CH_2), 35.6 (CH_2), 22.7 (CH_2), 21.7 (Ar-CH_3), 1 C=O and 1 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{25}H_{26}N_2O_5S$ $[M+Na]^+$ 489.1455; found 489.1455.



Benzyl 1-(5-oxo-5-phenylpentyl)-2-tosylhydrazine-1-carboxylate (319). Hydrazine **240**[95] (200 mg, 0.48 mmol, 1.0 equiv), 5-hydroxy-1-phenylpentan-1-one[101] (84 mg, 0.48 mmol, 1.0 equiv), triphenylphosphine (188 mg, 0.72 mmol, 1.5 equiv), diethyl azodicarboxylate (112 µL, 0.72 mmol, 1.5 equiv) and tetrahydrofuran (4.8 mL, 0.1 M) were combined and stirred at room temperature for 24 h. The reaction mixture was then concentrated *in vacuo*. The crude product was purified by column chromatography (30% EtOAc/ pet ether) to give the tetrasubstituted hydrazide. To this hydrazide was added trifluoroacetic acid (368 µL, 4.8 mmol, 10.0 equiv) and dichloromethane (4.8 mL, 0.1 M), the solution was then stirred for 2 h. The resulting yellow solution

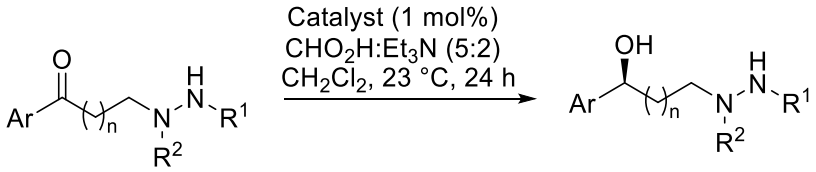
was concentrated *in vacuo* to give a yellow oil, which was purified by column chromatography (25% EtOAc/pet ether) to yield **319** as a white solid (140 mg, 0.29 mmol, 61%). R_f = 0.28 (25% EtOAc in petroleum ether); M.p. 86-88 °C; IR (film) 3214, 2957, 1699, 1671, 1364, 1181 cm^{-1}; δH (500 MHz; $CDCl_3$) 7.96 (2H, d, *J* 7.6, Ar-H), 7.74 (2H, d, *J* 8.0, Ar-H), 7.59 (1H, t, *J* 7.3, Ar-H), 7.49 (2H, t, *J* 7.7, Ar-H), 7.38-7.30 (3H, m, Ar-H), 7.22 (2H, d, *J* 8.0, Ar-H), 7.15 (2H, s, Ar-H), 6.99 (1H, s, NH), 4.90 (2H, br s, $COOCH_2$), 3.72 (2H, br s, CH_2NCbz), 2.99 (2H, br s, $COCH_2$), 2.42 (3H, s, CH_3), 1.79-1.67 (4H, m, $COCH_2C\mathit{H}_2C\mathit{H}_2$); δC (125 MHz, $CDCl_3$) 199.8 (C=O), 144.5 (Ar-C), 136.9 (Ar-C), 135.2 (Ar-C), 133.1 (Ar-CH), 129.5 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 68.4 (CH_2), 50.7 (CH_2), 37.9 (CH_2), 26.5 (CH_2), 21.7 (Ar-CH_3), 20.9 (CH_2), 1 C=O, 1 Ar-C and 1 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{26}H_{28}N_2O_5S$ $[M+Na]^+$ 503.1611; found 503.1615.



Benzyl 1-(6-oxo-6-phenylhexyl)-2-tosylhydrazine-1-carboxylate (320). Hydrazine **240**[95] (500 mg, 1.19 mmol, 1.0 equiv), 6-hydroxy-1-phenylhexan-1-one[101] (229 mg, 1.19 mmol, 1.0 equiv), triphenylphosphine (780 mg, 2.98 mmol, 2.5 equiv), diethyl azodicarboxylate (462 µL, 2.98 mmol, 2.5 equiv) and THF (12 mL, 0.1 M) were stirred at rt for 24 h. The reaction mixture was then concentrated *in vacuo*. The crude product was purified by column chromatography (30% EtOAc/ pet ether) to give the tetrasubstituted hydrazide. To this hydrazide was added trifluoroacetic acid (912 µL, 11.9 mmol, 10.0 equiv) and dichloromethane (11.9 mL, 0.1 M), the solution was then stirred for 2 h. The resulting yellow solution was concentrated *in vacuo* to give a yellow oil, which was purified by column chromatography (25% EtOAc/pet ether) to yield **320** as a colourless oil (204 mg, 0.41 mmol , 35%). R_f = 0.32 (25% EtOAc in petroleum ether). IR (film) 3219, 235, 1711, 1681, 1339, 1159 cm^{-1}; δH (500 MHz; $CDCl_3$) 7.95 (2H, d, *J* 7.4, Ar-*H*), 7.71 (2H, d, *J* 8.0, Ar-CH), 7.56 (1H, t, J 7.3, Ar-*H*), 7.47 (2H, t, *J* 7.7, Ar-CH), 7.34-7.29 (3H, m, Ar-CH), 7.20 (2H, d, *J* 8.1, Ar-CH), 7.12 (2H, br s, Ar-

CH), 6.93 (1H, br s, NH), 4.88 (2H, br s, CH_2Ph), 3.65 (2H, br s, NC*H*$_2$), 2.93 (2H, t, *J* 7.2, CH_2CO), 2.40 (3H, s, CH_3), 1.75-1.62 (4H, m, 2 x CH_2), 1.31 (2H, pentet, *J* 7.6, CH_2); δC (125 MHz; $CDCl_3$) 200.2 (C=O), 144.5 (Ar-C), 136.9 (Ar-C), 133.0 (Ar-CH), 129.5 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 68.3 (CH_2), 64.3 (CH_2), 50.9 (CH_2), 38.2 (CH_2), 26.1 (CH_2), 23.8 (CH_2), 21.7 (CH_3), C=O, 2 Ar-C, and 2 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{27}H_{30}N_2O_5S$ $[M+Na]^+$ 517.1768; found 517.1767.

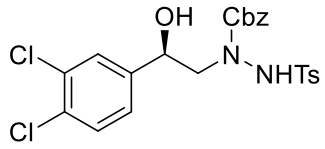
General procedure 6: Asymmetric Transfer Hydrogenation (ATH)



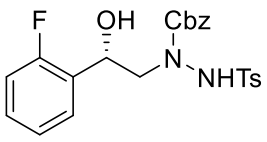
Scheme 6.3 General procedure for the ATH reaction.

A solution of catalyst (0.5 - 1 mol%) in formic acid : triethylamine (5 : 2) azeotrope (so that [S] = 1.0 M) was stirred for 15 min. The ketone substrate (1.0 equiv) and Dichloromethane (so that [S] = 0.25 – 0.5 M) were added and stirred at 23 °C. After 24 h, the reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (35-40% EtOAc/ pet ether) to give the following alcohols.

In order to synthesise racemic samples of these compounds to determine ee, there were two methods employed. Either general method 3 was repeated with the opposite catalyst enantiomer and the two products obtained were mixed to generate a pseudo-racemate. Alternatively the ketones were reduced to the racemic alcohols. The ketone substrate (1.0 equiv), methanol (so that [S] = 0.1 M) and sodium borohydride (2.5 equiv) were stirred at rt. After 2 h the solution was quenched with water (10 mL), washed with dichloromethane (3 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography using the same conditions reported below for each compound.

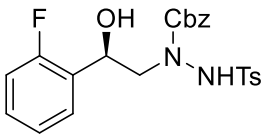


Benzyl (*R*)-1-(2-(3,4-dichlorophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (260). Following general procedure 6, aryl ketone **249** (100 mg, 0.20 mmol, 1.0 equiv), catalyst (*S*,*S*)-**233**[93] (1.2 mg, 2.0 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.2 mL, 1 M) and dichloromethane (0.4 mL, 0.5 M) yielded **260** as a white solid (100 mg, 0.2 mmol, 99%). M.p. 141-142 °C; R_f = 0.21 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ –37.7 (*c* 0.12, $CHCl_3$). Enantiomeric excess (92% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 12/88; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 18.4 min; t_R 24.1 min; IR (film) 3424, 3118, 2968, 2891, 1715, 1466, 1394, 1203 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.73 (2H, d, *J* 8.0, Ar-H), 7.45 (1H, s, Ar-H), 7.40 (1H, d, *J* 8.2, Ar-H), 7.36-7.32 (3H, m, Ar-H), 7.22 (2H, d, *J* 8.1, Ar-H), 7.19-7.05 (4H, m, Ar-H), 5.12 (1H, dd, *J* 9.1, 2.1, C*H*OH), 4.87 (2H, br s, CH_2Ph), 3.81 (1H, t, *J* 8.9, NC*H*H), 3.71 (1H, d, *J* 13.8, NCH*H*) 2.42 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 144.9 (Ar-C), 141.2 (Ar-C), 132.8 (Ar-C), 131.9 (Ar-C), 130.6 (Ar-CH), 129.7 (Ar-CH), 129.7 (Ar-C, seen on HMBC), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 125.3 (Ar-CH), 70.5 (CH, seen on HSQC), 68.9 (CH_2), 58.7 (CH_2), 21.8 (CH_3), 1 Ar-C, C=O not seen; HRMS (ESI^+) calculated for $C_{23}H_{22}{}^{35}Cl_2N_2O_5S$ $[M+Na]^+$ 531.0519; found 531.0517.

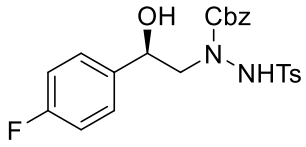


Benzyl (*S*)-1-(2-(2-fluorophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (261). Following general procedure 6, aryl ketone **250** (100 mg, 0.22 mmol, 1.0 equiv), catalyst (*R*,*R*)-**247**[96] (1.5 mg, 2.2 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.22 mL, 1.0 M) and dichloromethane (0.44 mL, 0.5 M) yielded **261** as a colourless oil (97 mg, 0.21 mmol, 97%). R_f = 0.21 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +4.0 (*c* 0.22, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 56.4 min; t_R 61.4 min. IR (film) 3503, 3237, 2926, 1713, 1305, 1128 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.73 (2H, d, *J* 7.9, Ar-CH), 7.47 (1H, t, *J* 7.3, Ar-H),

7.42 (1H, d, *J* 7.7, Ar-H), 7.38-7.26 (3H, m, Ar-H), 7.20 (2H, d, *J* 8.0, Ar-H), 7.18-7.11 (3H, m, Ar-H), 7.00 (1H, t, *J* 10.0, Ar-H), 5.44-5.34 (1H, m, C*H*OH), 4.86 (2H, br s, C*H*$_2$Ph), 3.99-3.89 and 2.95-2.75 (minor rotamer) (2H, m, NCH$_2$) 2.40 (3H, s, CH$_3$); δ*C* (125 MHz; CDCl$_3$) 159.9 (d, *J* 245.0, Ar-CF), 144.6 (Ar-C), 135.0 (Ar-C), 129.6 (Ar-CH), 129.6 (Ar-CH), 128.0 (d, *J* 12.5, Ar-C), 127.7 (d, *J* 3.8, Ar-CH), 124.5 (d, *J* 3.8, Ar-CH), 115.4 (d, *J* 21.3, Ar-CH), 68.7 (CH$_2$), 66.3 (CH, seen on HSQC), 57.0 (CH$_2$), 21.7 (CH$_3$), 1 Ar-C, 4 Ar-CH, C=O not seen; δ*F* (376 MHz, CDCl$_3$) -118.6 (CF); HRMS (ESI$^+$) calculated for $C_{23}H_{23}FN_2O_5S$ $[M+Na]^+$ 481.1204; found 481.1209.

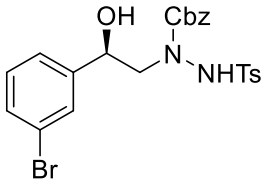


Benzyl (*R*)-1-(2-(2-fluorophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (261). Following general procedure 6, aryl ketone **250** (100 mg, 0.22 mmol, 1.0 equiv), catalyst (*S*,*S*)-**233**[93] (1.5 mg, 2.2 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.22 mL, 1.0 M) and dichloromethane (0.44 mL, 0.5 M) yielded **261** as a colourless oil (97 mg, 0.21 mmol, 97%). $[\alpha]^{32}_D$ –3.17 (*c* 0.30, CHCl$_3$). Enantiomeric excess (77% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 56.4 min; t_R 61.4 min.

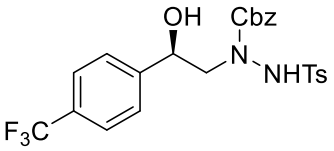


Benzyl (*R*)-1-(2-(4-fluorophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (263) Following general procedure 6, aryl ketone **252** (106 mg, 0.23 mmol, 1.0 equiv), catalyst (*S*,*S*)-**233**[93] (1.4 mg, 2.3 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.23 mL, 1.0 M) and dichloromethane (0.46 mL, 0.5 M) yielded **263** as a white solid (105 mg, 0.23 mmol, 99%). M.p. 122-124 °C. $[\alpha]^{32}_D$ – 29.9 (*c* 0.09, CHCl$_3$). Enantiomeric excess (99% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 5/95; flow rate = 1 mL/min; detection wavelength = 254 nm] t_R 42.9 min: t_R 47.5 min. IR (film) 3447, 3263, 3129, 2923, 1717, 1601, 1508, 1398, 1217 cm^{-1}; δH (500 MHz, CDCl$_3$) 7.72 (2H, dd, *J* 8.2, 3.3, Ar-CH), 7.36-7.27 (5H, m, Ar-CH), 7.25-7.06 (4H, m, Ar-CH), 7.02 (2H, t, *J*

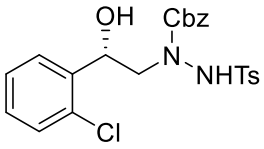
8.5, Ar-CH), 5.13 (1H, d, *J* 9.0, C*H*OH), 4.95-4.72 (2H, m, CH_2Ph), 3.86 and 3.17 (minor rotamer) (1H, m, NCH_2), 3.73 and 3.00 (minor rotamer) (1H, m, NCH_2), 2.41 and 2.43 (minor rotamer) (3H, s, CH_3); δC (150 MHz; $CDCl_3$) 162.5 and 162.6 (minor rotamer) (d, *J* 245.0, Ar-CF), 144.7 (Ar-C), 143.7 (Ar-C) 136.8 and 136.6 (minor rotamer) (d, *J* 3.8, Ar-C), 136.7 (Ar-C), 129.8 (Ar-CH), 129.6 (Ar-CH), 128.5 and 128.4 (minor rotamer) (Ar-CH), 128.1 (Ar-CH), 127.7 and 127.6 (minor rotamer) (d, *J* 7.5, Ar-CH), 127.1 (Ar-CH), 115.5 and 115.6 (minor rotamer) (d, *J* 21.3, Ar-CH), 72.2 (CH), 68.7 (CH_2), 58.5 and 50.2 (minor rotamer) (CH_2), 21.7 (CH_3); δF (376 MHz, $CDCl_3$) -114.1 and -113.7 (minor rotamer) (CF); HRMS (ESI^+) calculated for $C_{24}H_{23}F_3N_2O_5S$ $[M+Na]^+$ 531.1172; found 531.1173.



Benzyl (*R*)-1-(2-(3-bromophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (264). Following general procedure 6, aryl ketone **253** (80 mg, 0.15 mmol, 1.0 equiv), catalyst (*S*,*S*)-**233**[93] (1.0 mg, 1.5 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.15 mL, 1.0 M) and dichloromethane (0.3 mL, 0.5 M) yielded **264** as a white solid (80 mg, 0.15 mmol, 99%). R_f = 0.20 (35% EtOAc in petroleum ether); M.p. 135-136 °C; $[\alpha]^{32}_D$ –16.0 (*c* 0.50, $CHCl_3$); Enantiomeric excess (97% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 9/91; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 19.6 min; t_R 25.1 min; IR (film) 3456, 3222, 2929, 1715, 1323, 1211, 1185 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.73 (2H, d, *J* 8.0, Ar-CH), 7.50 (1H, s, Ar-H), 7.42 (1H, d, *J* 7.7, Ar-H), 7.36-7.32 (3H, m, Ar-H), 7.27-7.05 (6H, m, Ar-H) 5.11 (1H, d, *J* 9.5, C*H*OH), 4.87 (2H, br s, CH_2Ph), 3.90-3.65 (2H, m, NCH_2) 2.41 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 144.8 (Ar-C), 143.4 (Ar-C), 131.1 (Ar-CH), 130.2 (Ar-CH), 129.7 (Ar-CH), 129.0 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 124.6 (Ar-CH), 122.8 (Ar-C), 70.6 (CH, seen on HSQC), 68.8 (CH_2), 58.5 (CH_2), 21.8 (CH_3), 2 Ar-C, 1 Ar-CH, C=O not seen; HRMS (ESI^+) calculated for $C_{23}H_{23}{}^{79}BrN_2O_5S$ $[M+Na]^+$ 541.0403; found 541.0411.

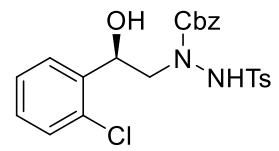


Benzyl (*R*)-1-(2-hydroxy-2-(4-(trifluoromethyl)phenyl)ethyl)-2-tosylhydrazine-1-carboxylate (265). Following general procedure 6, aryl ketone **254** (100 mg, 0.20 mmol, 1.0 equiv), catalyst (*S*,*S*)-**233**[93] (1.2 mg, 2.0 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.2 mL, 1.0 M) and dichloromethane (0.4 mL, 0.5 M) yielded **265** as a white solid (97 mg, 0.19 mmol, 96%). R_f = 0.19 (35% EtOAc in petroleum ether); M.p. 147-148 °C; $[\alpha]^{32}_D$ –18.1 (*c* 0.06, $CHCl_3$). Enantiomeric excess (95% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 8/92; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 20.6 min; t_R 25.4 min; IR (film) 3439, 3144, 2923, 1716, 1401, 1324, 1087 cm^{-1}; δ*H* (600 MHz; d6-DMSO at 100 °C) 9.66 (1H, s, NH), 7.68 (2H, d, *J* 8.2, Ar-H), 7.61 (2H, d, *J* 8.1, Ar-H), 7.50 (2H, d, *J* 8.0, Ar-H), 7.39-7.25 (5H, m, Ar-H), 7.15 (2H, d, *J* 7.5, Ar-H), 5.31 (1H, s, OH), 4.96-4.92 (1H, t, *J* 8.2, C*H*OH), 4.75-4.63 (2H, m, CH_2Ph), 3.75-3.58 (2H, m, NCH_2), 2.38 (3H, s, CH_3); δ*C* (150 MHz; D6-DMSO at 100 °C) 155.7 (C=O), 148.1 (Ar-C), 143.9 (Ar-C), 137.3 (Ar-C), 136.3 (Ar-C), 129.8 (Ar-CH), 128.6 (q, *J* 26.3, Ar-C), 128.5 (Ar-CH), 128.2 (Ar-CH), 127.9 (Ar-CH), 127.9 (Ar-CH), 127.3 (Ar-CH), 125.3 (q, *J* 3.8, Ar-CH), 124.8 (q, *J* 225.0, CF_3), 69.5 (CH), 67.7 (CH_2), 58.0 (CH_2), 21.4 (CH_3); δ*F* (286 MHz, D6-DMSO) -61.8 (CF_3); HRMS (ESI^+) calculated for $C_{24}H_{23}F_3N_2O_5S$ $[M+Na]^+$ 531.1172; found 531.1173.

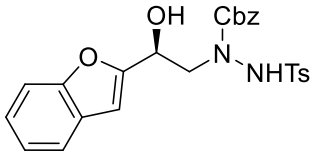


Benzyl (*S*)-1-(2-(2-chlorophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (266). Following general procedure 6, aryl ketone **255** (100 mg, 0.20 mmol, 1.0 equiv), catalyst (*R*,*R*)-**247**[96] (1.3 mg, 2.0 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.2 mL, 1.0 M) and dichloromethane (0.4 mL, 0.5 M) yielded **266** as a colourless oil (100 mg, 0.2 mmol, 99%). R_f = 0.21 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +35.8 (*c* 0.12, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254

nm] t_R 57.1 min; t_R 65.2 min; IR (film) 3443, 3115, 2896, 1717, 1457, 1432, 1250 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.74 (2H, d, *J* 7.8, Ar-H), 7.57 (1H, d, *J* 7.5, Ar-H), 7.40 (1H, d, *J* 8.2, Ar-H), 7.35-7.10 (9H, m, Ar-H), 5.48 (1H, m, C*H*OH), 4.88 (2H, br s, C*H*$_2$Ph), 3.87 and 2.92 (minor rotamer) (2H, br s, NCH_2), 2.40 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 144.6 (Ar-C), 138.4 (Ar-C), 131.9 (Ar-C), 129.6 (Ar-CH), 129.5 (Ar-CH), 129.1 (Ar-CH), 128.5 (Ar-CH), 128.2 (Ar-CH), 127.6 (Ar-CH), 127.2 (Ar-CH), 69.0 (CH, seen on HSQC), 68.7 (CH_2), 56.6 (CH_2), 21.7 (CH_3), 2 Ar-C, 2 Ar-CH, C=O not seen; HRMS (ESI^+) calculated for $C_{23}H_{24}{}^{35}ClN_2O_5S$ $[M+Na]^+$ 497.0908; found 497.0905.

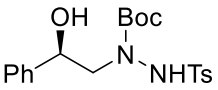


Benzyl (*R*)-1-(2-(2-chlorophenyl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (266). Following general procedure 6, aryl ketone **255** (100 mg, 0.20 mmol, 1.0 equiv), catalyst (*S*,*S*)-**233**[93] (1.3 mg, 2.0 μmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.2 mL, 1.0 M) and dichloromethane (0.4 mL, 0.5 M) yielded **266** as a colourless oil (100 mg, 0.2 mmol, 99%). $[\alpha]^{32}_D$ – 14.7 (*c* 0.10, $CHCl_3$). Enantiomeric excess (19% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 57.1 min; t_R 65.2 min.

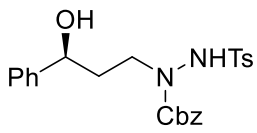


Benzyl (*R*)-1-(2-(benzofuran-2-yl)-2-hydroxyethyl)-2-tosylhydrazine-1-carboxylate (269) Following general procedure 6, aryl ketone **258** (70 mg, 0.15 mmol), catalyst (*S*,*S*)-**233**[93] (0.96 mg, 0.0015 mmol), 5:2 FA:TEA complex (0.15 mL, 1 M) and CH_2Cl_2 (0.3 mL, 0.5 M) yielded **269** as a colourless oil (64 mg, 0.13 mmol, 91%). $[\alpha]^{32}_D$ – 2.62 (c 0.21, $CHCl_3$). Enantiomeric excess (99% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 10/90; flow rate = 1 mL/min; detection wavelength = 254 nm] t_R 24.8 min: t_R 29.1 min. IR (film) 3456, 3222, 2929, 1715, 1323, 1211, 1185 cm^{-1}; δH (500 MHz; $CDCl_3$) 7.72 (2H, d, *J* 7.9, Ar-H), 7.43 (1H, d, *J* 7.6, Ar-H) 7.42 (1H, d, *J* 8.1, Ar-H), 7.36-7.05 (9H, m, Ar-H), 6.67 (1H, s, Ar-H), 5.22 (1H, dd, *J* 8.5, 3.6, C*H*OH), 4.82

(2H, br s, C*H*$_2$Ph), 4.29-3.90 (2H, m, NCH$_2$) 2.39 (3H, s, CH$_3$); δC (125 MHz; CDCl$_3$) 156.1 (Ar-C), 154.9 (Ar-C), 144.6 (Ar-C), 130.6 (Ar-CH), 129.6 (Ar-CH) 128.5 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-C) 124.5 (Ar-CH), 123.0 (Ar-CH), 121.2 (Ar-CH), 111.3 (Ar-CH), 103.9 (Ar-CH) 68.7 (CH$_2$), 65.5 (CH, seen on HSQC), 55.4 (CH$_2$), 21.7 (CH$_3$), 3 Ar-C, 2 Ar-CH, C=O not seen; HRMS (ESI$^+$) calculated for $C_{25}H_{24}N_2O_6S$ [M+Na]$^+$ 503.1247; found 503.1249.

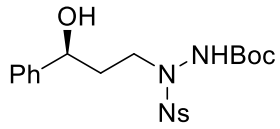


***tert*-Butyl (*R*)-1-(2-hydroxy-2-phenylethyl)-2-tosylhydrazine-1-carboxylate (211).** Following general procedure 6, aryl ketone **283** (100 mg, 0.25 mmol, 1.0 equiv), (*S*,*S*)-**233**[93] (1.6 mg, 2.5 µmol, 0.01 equiv), 5:2 FA:TEA complex (0.25 mL, 1 M) and CH_2Cl_2 (0.50 mL, 0.5 M) yielded **211** as a white solid (100 mg, 0.25 mmol, 99%). R_f = 0.21 (25% EtOAc in petroleum ether); M.p. 138-139 °C; $[\alpha]_D^{28}$ = –4.8 (*c* 0.12, $CHCl_3$); Enantiomeric excess (99% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 1.5/98.5; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 37.7 min; t_R 42.4 min; IR (film) 3456, 3128, 2975, 1709, 1089; δ*H* (500 MHz, $CHCl_3$) 7.82 (2H, d, *J* 8.2, Ar-H), 7.36 (7H, m, Ar-H), 5.17 (1H, dd, *J* 9.9, 3.6, CHPh), 3.86 (1H, br m, NC*H*H), 3.74 (1H, d, *J* 9.9, NCH*H*), 2.44 (3H, s, CH_3), 1.18 (9H, br s, $C(CH_3)_3$); δ*C* (125 MHz, $CDCl_3$) 144.6 (C=O), 141.4 (Ar-C), 132.2 (Ar-C), 132.1 (Ar-C) 130.0 (Ar-CH), 129.8 (Ar-CH), 128.6 (Ar-CH), 128.0 (Ar-CH), 126.0 (Ar-CH), 82.9 (C), 75.2 (CH), 58.8 (CH_2) 27.8 (CH_3), 21.6 (CH_3); HRMS (ES$^+$) calculated for $C_{20}H_{26}N_2O_5S$ (M+Na)$^+$ 429.1451; found 429.1455.

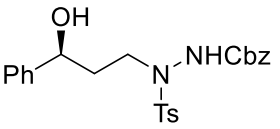


Benzyl (*S*)-1-(3-hydroxy-3-phenylpropyl)-2-tosylhydrazine-1-carboxylate (298). Following general procedure 6, aryl ketone **287** (100 mg, 0.22 mmol), catalyst (*S*,*S*)-**233**[93] (1.4 mg, 2.2 µmol), 5 : 2 formic acid : triethylamine complex (0.22 mL, 1.0 M) and dichloromethane (0.88 mL, 0.25 M) yielded **298** as a colourless oil (100 mg, 0.22 mmol, 99%). R_f = 0.23 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ –4.6 (*c* 0.75, $CHCl_3$). Enantiomeric excess was determined after

cyclisation to **309**. IR (film) 3503, 3228, 2951, 1707, 1340, 1185 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.73 (2H, d, *J* 7.9, Ar-CH), 7.38-7.29 (5H, m, Ar-H) 7.47 (4H, dd, *J* 13.5 and 7.9, Ar-H), 7.21 (3H, d, *J* 7.9, Ar-H), 7.02 (1H, br s, NH), 5.01-4.59 (3H, m, C*H*OH and CH_2Ph), 3.84 (2H, br s, NCH_2), 2.42 (3H, s, CH_3) 2.09-2.03 (2H, m, C*H*$_2$CHOH); δ*C* (125 MHz; $CDCl_3$) 144.4 (Ar-C), 143.4 (Ar-C), 135.1 (Ar-C), 129.5 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.1 (Ar-CH), 127.8 (Ar-CH), 125.6 (Ar-CH), 72.3 (CH), 68.4 (CH_2), 48.7 (CH_2), 35.0 (CH_2), 21.7 (CH_3), C=O and 1 Ar-C not seen; HRMS (ESI^+) calculated for $C_{24}H_{26}N_2O_5S$ $[M+Na]^+$ 477.1455; found 477.1457.

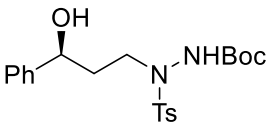


***tert*-Butyl (*S*)-2-(3-hydroxy-3-phenylpropyl)-2-((4-nitrophenyl)sulfonyl)-hydrazine-1-carboxylate (296).** Following general procedure 6, aryl ketone **285** (100 mg, 0.22 mmol, 1.0 equiv), catalyst (*S*,*S*)-**233**[93] (1.4 mg, 2.2 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.22 mL, 1.0 M) and dichloromethane (0.88 mL, 0.25 M) yielded **296** as a white solid (86 mg, 0.19 mmol, 86%). R_f = 0.18 (35% EtOAc in petroleum ether); M.p. 112-114 °C; $[\alpha]^{32}_D$ –5.0 (*c* 0.30, $CHCl_3$); enantiomeric excess was determined after cyclisation to **307**. IR (film) 3512, 3287, 2951, 1712, 1620, 1350, 1158 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 8.28 (2H, d, *J* 8.3, Ar-H), 8.04 (2H, t, *J* 9.2, Ar-H), 7.29 (3H, d, *J* 4.3, Ar-H), 7.28-7.19 (2H, m, Ar-H), 6.62 (1H, s, NH), 4.84 (1H, t, *J* 6.1, C*H*OH), 3.84-3.45 (2H, m, NCH_2), 1.95 (2H, q, *J* 6.1, C*H*$_2$CHOH), 1.26-1.18 (9H, m, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 153.5 (C=O), 150.5 (Ar-C), 143.9 (Ar-C), 128.7 (Ar-CH), 128.6 (Ar-CH), 127.8 (Ar-CH), 125.7 (Ar-CH), 124.0 (Ar-CH), 83.3 (C) and 82.6 (minor rotamer), 71.7 (CH), 47.5 (CH_2), 36.4 (CH_2), 27.9 (CH_3) and 27.8 (minor rotamer), 1 Ar-C not seen; HRMS (ESI^+) calculated for $C_{20}H_{25}N_3O_7$ $[M+Na]^+$ 474.1305; found 474.1307.



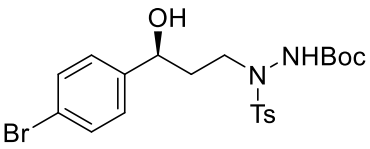
Benzyl (*S*)-2-(3-hydroxy-3-phenylpropyl)-2-tosylhydrazine-1-carboxylate (**295**) Following general procedure 6, aryl ketone **284** (1.0 g, 2.20 mmol, 1.0 equiv), (*S*,*S*)-**233**[93] (7.0 mg, 11 µmol, 0.005 equiv) and formic acid :

trimethylamine (5 : 2) azeotrope (2.2 mL, 1M) and dichloromethane (8.8 mL, 0.25 M) were stirred for 72 h gave **295** as a white solid (1.00 g, 2.20 mmol, 99%). R_f = 0.28 (33% EtOAc in petroleum ether). M.p. 125-127 °C. $[\alpha]^{32}_D$ – 15.24 (c 0.08, $CHCl_3$). Enantiomeric excess was determined after cyclisation to **306**. IR (film) 3546, 3313, 2925, 1749, 1220, cm^{-1}; δH (500 MHz; $CDCl_3$) 7.76 (2H, d, *J* 6.2, Ar-CH), 7.37-7.22 (12H, m, Ar-H) 6.57 (1H, br s, NH), 5.10-4.90 (3H, m, C*H*OH and CH_2Ph), 3.71 (1H, br s, NC*H*H), 3.44 (1H, br s, NCH*H*), 2.64 (1H, br s, CHOHC*H*H), 2.42 (3H, s, CH_3) 1.95 (1H, br s, CHOHCH*H*); δC (125 MHz; $CDCl_3$) 154.8 (C=O), 144.7 (Ar-C), 143.2 (Ar-C), 135.4 (Ar-C), 133.4 (Ar-C), 129.8 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.5 (Ar-CH) 128.2 (Ar-CH), 127.5 (Ar-CH), 125.7 (Ar-CH), 71.4 (CH), 67.8 (CH_2), 48.0 (CH_2), 36.4 (CH_2), 21.7 (CH_3), 1 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{24}H_{26}N_2O_5S$ $[M+Na]^+$ 477.1455; found 4771453.

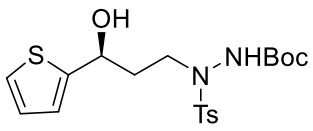


***tert*-Butyl (*S*)-2-(3-hydroxy-3-phenylpropyl)-2-tosylhydrazine-1-carboxylate (297).** Following general procedure 6, aryl ketone **286** (97 mg, 0.23 mmol, 1.0 equiv), catalyst (*S*,*S*)-**233**[93] (1.4 mg, 2.3 μmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.23 mL, 1.0 M) in dichloromethane (0.92 mL, 0.25 M) yielded **297** as a colourless oil (96 mg, 0.23 mmol, 98%). R_f = 0.22 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ –34.4 (*c* 0.20, $CHCl_3$). Enantiomeric excess (96% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 15/85; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 15.4 min; t_R 20.1 min; IR (film) 3294, 2985, 1745, 1393, 1159, 1055 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.81-7.79 (2H, m, Ar-*H*), 7.38-7.27 (7H, m, Ar-*H*), 6.45 (major) and 6.08 (minor) (1H, br s, N*H*), 4.97 (1H, br s, C*H*OH), 3.68-3.48 (2H, m, NCH_2), 2.95 (1H, br s, O*H*), 2.42 (3H, s, Ts-CH_3), 1.97 (2H, br s, CHCH_2), 1.32 (9H, s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 153.9 (C=O), 144.7 (Ar-C), 144.6 (Ar-C), 133.8 (Ar-C), 129.7 (Ar-CH), 128.8 (Ar-CH), 128.6 (Ar-CH), 127.5 (Ar-CH), 125.8 (Ar-CH), 81.9 (C), 71.5 (CH), 47.8 (N*C*H_2), 36.6 (CH_2),

28.0 (CH_3), 21.8 (CH_3); HRMS (ESI^+) calculated for $C_{21}H_{28}N_2NaO_5S$ $[M+Na]^+$ 443.1611; found 443.1610.

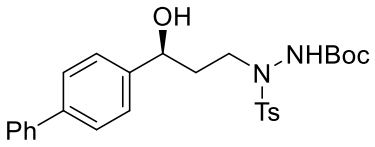


***tert*-Butyl (*S*)-2-(3-(4-bromophenyl)-3-hydroxypropyl)-2-tosylhydrazine-1-carboxylate (299).** Following general procedure 6, aryl ketone **288** (100 mg, 0.20 mmol, 1.0 equiv), catalyst (*S*,*S*)-**233**[93] (1.27 mg, 2.0 µmol), 5 : 2 formic acid : triethylamine complex (0.20 mL, 1.0 M) and dichloromethane (0.80 mL, 0.25 M) yielded **299** as a white solid (100 mg, 0.20 mmol, 99%). M.p. 121-124 °C; R_f = 0.17 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ –25.8 (*c* 0.65, $CHCl_3$). Enantiomeric excess (91% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 25.0 min; t_R 30.2 min. IR (film) 3513, 3303, 2925, 1704, 1367, 1247 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.83 (2H, d, *J* 7.1, Ar-CH), 7.48 (2H, d, *J* 7.8, Ar-H), 7.36 (2H, d, *J* 7.7, Ar-H), 7.36 (2H, d, *J* 7.6, Ar-H), 5.02 (1H, br s, C*H*OH), 3.88-3.01 (2H, m, NCH_2), 2.46 (3H, s, CH_3) 2.05-1.82 (2H, m, C*H*$_2$CHOH), 1.36 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 154.1 (C=O), 144.8 (Ar-C), 143.6 (Ar-C), 133.5 (Ar-C), 131.5 (Ar-CH), 129.7 (Ar-CH), 128.7 (Ar-CH), 127.5 (Ar-CH), 121.0 (Ar-C), 82.1 (C), 70.8 (CH), 47.8 (CH_2), 36.5 (CH_2), 27.9 (CH_3), 21.6 (CH_3); HRMS (ESI^+) calculated for $C_{21}H_{27}{}^{79}BrN_2O_5S$ $[M+Na]^+$ 521.0716; found 521.0716.

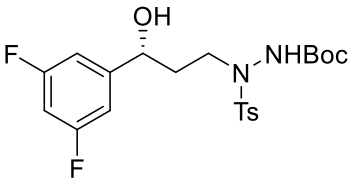


***tert*-Butyl (*S*)-2-(3-hydroxy-3-(thiophen-2-yl)propyl)-2-tosylhydrazine-1-carboxylate (300).** Following general procedure 6, aryl ketone **289** (100 mg, 0.24 mmol, 1.0 equiv), catalyst (*S*,*S*)-**233**[93] (1.5 mg, 2.4 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.24 mL, 1.0 M) and Dichloromethane (0.48 mL, 0.25 M) yielded **300** as a colourless oil (97 mg, 0.23 mmol, 97%). R_f = 0.21 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ –6.5 (*c* 0.13, $CHCl_3$). Enantiomeric excess (98% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min;

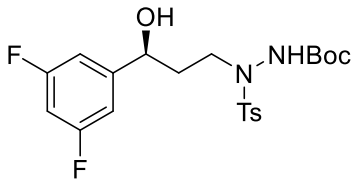
detection wavelength = 254 nm] t_R 22.4 min; t_R 24.5 min; IR (film) 3453, 3309, 2926, 1704, 1354, 1252 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.82 (2H, d, *J* 7.4, Ar-CH), 7.35 (2H, d, *J* 6.6, Ar-H), 7.26 (1H, d, *J* 4.0, Ar-H), 7.08-6.94 (2H, m, Ar-H), 6.43 (1H, s, NH), 5.27 (1H, br s, C*H*OH), 3.79-3.47 (2H, m, NCH_2), 2.45 (3H, s, CH_3) 2.20-2.03 (2H, m, CH_2CHOH), 1.34 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 153.8 (C=O), 148.4 (Ar-C), 144.6 (Ar-C), 133.7 (Ar-C), 129.6 (Ar-CH), 128.7 (Ar-CH), 126.7 (Ar-CH), 124.4 (Ar-CH), 123.5 (Ar-CH), 82.0 (C), 67.7 (CH), 47.6 (CH_2), 36.6 (CH_2), 27.9 (CH_3), 21.6 (CH_3); HRMS (ESI^+) calculated for $C_{19}H_{26}N_2O_5S_2$ $[M+Na]^+$ 449.1175; found 449.1179.



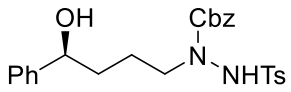
***tert*-Butyl (*S*)-2-(3-([1,1'-biphenyl]-4-yl)-3-hydroxypropyl)-2-tosylhydrazine-1-carboxylate (301).** Following general procedure 6, aryl ketone **290** (100 mg, 0.20 mmol, 1.0 equiv), catalyst (*S*,*S*)-**233**[93] (1.3 mg, 2.0 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.20 mL, 1.0 M) and Dichloromethane (0.80 mL, 0.25 M) yielded **301** as a white solid (100 mg, 0.20 mmol, 99%). M.p. 62-63 °C; R_f = 0.19 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ –17.7 (*c* 0.62, $CHCl_3$). Enantiomeric excess was determined after cyclisation to **312**. IR (film) 3513, 3303, 2926, 1704, 1391, 1247 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.84 (2H, d, *J* 7.1, Ar-CH), 7.60 (4H, t, *J* 7.1, Ar-H) 7.47 (4H, dd, *J* 13.5, 7.9, Ar-H), 7.36 (3H, t, *J* 7.5, Ar-H), 6.40 (1H, br s, NH), 5.07 (1H, s, C*H*OH), 3.81-3.42 (2H, m, NCH_2), 2.46 (3H, s, CH_3) 2.09-1.96 (2H, m, CH_2CHOH), 1.26 (9H, s, $C(CH_3)_3$); δC (125 MHz; $CDCl_3$) 153.9 (C=O), 150.5 (Ar-C), 144.6 (Ar-C), 143.5 (Ar-C), 140.3 (Ar-C), 133.7 (Ar-C), 129.7 (Ar-CH), 128.8 (Ar-CH), 128.7 (Ar-CH), 127.2 (Ar-CH), 127.2 (Ar-CH), 127.1 (Ar-CH), 126.2 (Ar-CH), 81.9 (C), 71.2 (CH), 47.8 (CH_2), 36.5 (CH_2), 28.0 (CH_3) 21.6 (CH_3); HRMS (ESI^+) calculated for $C_{27}H_{32}N_2O_5S$ $[M+Na]^+$ 519.1924; found 519.1924.



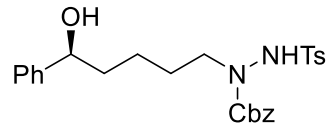
***tert*-Butyl (*R*)-2-(3-(3,5-difluorophenyl)-3-hydroxypropyl)-2-tosylhydrazine-1-carboxylate (302).** Following general procedure 6, aryl ketone **291** (572 mg, 1.26 mmol, 1.0 equiv), (*R*,*R*)-**247**[96] (8.4 mg, 13 µmol, 0.01 equiv), 5:2 formic acid : triethylamine complex (1.26 mL, 1 M) and CH_2Cl_2 (5 mL, 0.25 M) yielded **302** as a white solid (572 mg, 1.26 mmol, 99%). R_f = 0.46 (33% EtOAc in petroleum ether); $[\alpha]_D^{24}$ + 55.3 (*c* 0.03, $CHCl_3$); Enantiomeric excess (93% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 13.5 min; t_R 16.3 min. M.p. 110-111 °C; IR (film) 3333, 3165, 2980, 1740, 1625, 1183 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.84 (2H, d, *J* 7.4, Ar-H), 7.37 (2H, d, *J* 7.8, Ar-H), 6.95 (2H, d, *J* 6.3, Ar-H), 6.70 (1H, t, *J* 7.7, Ar-H), 6.33 (1H, s, NH), 5.08 (1H, d, *J* 5.1, C*H*OH), 3.79-3.65 (1H, br m, C*H*HN), 3.48-3.37 (1H, br m, CH*H*N), 2.46 (3H, s, C*H*$_3$), 2.04-1.95 (1H, br m, CHOHC*H*H), 1.92-1.79 (1H, br m, CHOHCH*H*), 1.37 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 163.1 (dd, *J* 246.2, 12.5, Ar-CF), 154.3 (C=O), 149.0 (Ar-C), 144.9 (Ar-C), 133.3 (Ar-C), 129.7 (Ar-CH), 128.7 (Ar-CH), 108.5 (dd, *J* 21.3, 6.3, Ar-CH), 102.4 (t, *J* 26.3, Ar-CH), 82.3 (C), 70.4 (CH), 47.8 (CH_2), 36.4 (CH_2), 27.9 (CH_3), 21.6 (CH_3); δ*F* (376 MHz; $CDCl_3$) -109.9 (Ar-CF); HRMS (ESI^+) calculated for $C_{21}H_{26}N_2NaO_5SF_2$ $[M+Na]^+$ 479.1423; found 479.1421.



***tert*-Butyl (*S*)-2-(3-(3,5-difluorophenyl)-3-hydroxypropyl)-2-tosylhydrazine-1-carboxylate (302).** Following general procedure 6, aryl ketone **291** (266 mg, 0.59 mmol, 1.0 equiv), (*S*,*S*)-**233**[93] (3.6 mg, 6 µmol, 0.01 equiv), 5:2 FA:TEA complex (0.59 mL, 1 M) and CH_2Cl_2 (2.4 mL, 0.25 M) yielded **302** as a white solid (266 mg, 0.59 mmol, 99%). $[\alpha]_D^{24}$ – 14.2 (*c* 0.10, $CHCl_3$); Enantiomeric excess (80% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 13.5 min; t_R 16.3 min.

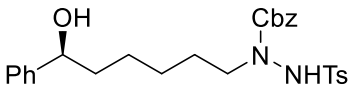


Benzyl (*S*)-1-(4-hydroxy-4-phenylbutyl)-2-tosylhydrazine-1-carboxylate (323). Following general procedure 6, aryl ketone **318** (60 mg, 0.13 mmol, 1.0 equiv), (*S*,*S*)-**233**[93] (1.0 mg, 1.3 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.13 mL, 1.0 M) and dichloromethane (0.26 mL, 0.5 M) yielded **323** as a colourless oil (60 mg, 0.13 mmol, 99%). R_f = 0.20 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ –13.0 (*c* 0.92, $CHCl_3$); enantiomeric excess was determined after cyclisation to **329**; IR (film) 3510, 3285, 2946, 1717, 1375, 1184 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.72 (2H, d, *J* 8.0, Ar-H), 7.40-7.30 (8H, m, Ar-H), 7.21 (2H, d, *J* 8.1, Ar-H), 7.12 (2H, d, *J* 6.1, Ar-H), 4.88 (2H, s, CH_2Ph), 4.69 (1H, s, C*H*OH), 3.70 (2H, br s, NCH_2), 2.42 (3H, s, CH_3), 1.85-1.62 (4H, m, CH_2CH_2CHOH); δ*C* (125 MHz; $CDCl_3$) 144.5 (Ar-C), 144.4 (Ar-C), 135.2 (Ar-C), 129.5 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 127.7 (Ar-CH), 125.8 (Ar-CH), 74.2 (CH), 68.4 (CH_2), 50.8 (CH_2), 35.7 (CH_2), 23.4 (CH_2), 21.7 (CH_3), C=O, 1 Ar-C and 1 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{25}H_{26}N_2O_5S$ $[M+Na]^+$ 489.1455; found 489.1455.



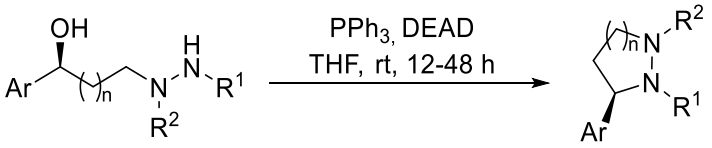
Benzyl (*S*)-1-(5-hydroxy-5-phenylpentyl)-2-tosylhydrazine-1-carboxylate (324). Following general procedure 6, aryl ketone **319** (80 mg, 0.17 mmol, 1.0 equiv), catalyst (*S*,*S*)-**233**[93] (1.0 mg, 1.7 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine complex (0.17 mL, 1.0 M) and dichloromethane (0.34 mL, 0.5 M) yielded **324** as a colourless oil (80 mg, 0.17 mmol, 99%). R_f = 0.20 (35% EtOAc in petroleum ether); $[\alpha]^{32}_D$ –8.2 (*c* 1.13, $CHCl_3$). Enantiomeric excess was determined after cyclisation to **330**; IR (film) 3489, 3233, 2925, 1707, 1340, 1215 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.72 (2H, d, *J* 8.0, Ar-H), 7.38-7.31 (8H, m, Ar-H), 7.21 (2H, d, *J* 8.1, Ar-H), 7.14 (2H, s, Ar-H), 6.91 (1H, s, NH), 4.88 (2H, s, CH_2Ph), 4.69-4.61 (1H, m, C*H*OH), 3.65 (2H, br s, NCH_2), 2.42 (3H, s, CH_3) 1.85-1.62 (4H, m, NCH_2CH_2 and CH_2CHOH), 1.42-1.31 (2H, m, $CH_2CH_2CH_2$); δC (125 MHz; $CDCl_3$) 144.6 (Ar-C), 144.5 (Ar-C), 135.2 (Ar-C), 129.5 (Ar-CH), 128.5 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 127.6 (Ar-

CH), 125.8 (Ar-CH), 74.3 (CH), 68.3 (CH_2), 50.9 (CH_2), 38.5 (CH_2), 26.7 (CH_2), 22.6 (CH_2), 21.7 (CH_3), 1 C=O, 1 Ar-C and 2 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{26}H_{30}N_2O_5S$ $[M+Na]^+$ 505.1768; found 505.1767.

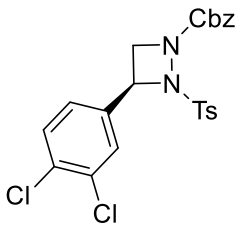


Benzyl (*S*)-1-(6-hydroxy-6-phenylhexyl)-2-tosylhydrazine-1-carboxylate (325). Following general procedure 6, aryl ketone **320** (93 mg, 0.17 mmol), (*S*,*S*)-**233**[93] (1.20 mg, 1.9 µmol), 5 : 2 formic acid : triethylamine complex (0.19 mL, 1 M) and dichloromethane (0.38 mL, 0.5 M) yielded **325** as a colourless oil (66.8 mg, 0.14 mmol, 71%). R_f = 0.47 (35% EtOAc in petroleum ether). $[\alpha]^{32}_D$ – 6.25 (c 0.02, $CHCl_3$). Enantiomeric excess could not be determined. IR (film) 3473, 3225, 2932, 1701, 1338, 1158 cm^{-1}; δH (500 MHz; $CDCl_3$) 7.70 (2H, d, *J* 8.0, Ar-CH), 7.38-7.27 (8H, m, Ar-H), 7.19 (2H, d, *J* 8.1, Ar-H), 7.11 (2H, s, Ar-H), 6.91 (1H, s, NH), 4.86 (2H, s, CH_2Ph), 4.63 (1H, t, *J* 7.0, C*H*OH), 3.61 (2H, br s, NCH_2), 2.4) 173.60 (3H, s, CH_3) 1.80-1.60 (4H, m, 2 x CH_2), 1.45-1.29 (4H, m, 2 x CH_2); δC (125 MHz, $CDCl_3$) 156.3 (C=O), 144.8 (Ar-C), 144.4 (Ar-C), 129.5 (Ar-CH), 128.5 (Ar-CH) 128.5 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 127.6 (Ar-CH), 125.9 (Ar-CH), 74.5 (CH), 68.3 (CH_2), 64.3 (CH_2), 51.0 (CH_2), 38.8 (CH_2), 26.3 (CH_2), 25.4 (CH_2), 21.7 (CH_3), 2 Ar-C and 2 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{27}H_{32}N_2O_5S$ $[M+Na]^+$ 519.1924; found 519.1922.

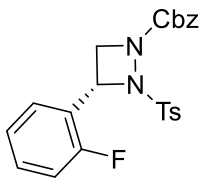
General procedure 7: Mitsunobu cyclisation



To a solution of alcohol (1.0 equiv) in tetrahydrofuran (0.01 M) was added triphenylphosphine (1.5-2.5 equiv) and diethyl azodicarboxylate (1.5-2.5 equiv). The reaction mixture was stirred at rt until completion of the reaction (12-48 h, monitored by TLC). The reaction mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (20-30% EtOAc in petroleum ether) to give the following compounds.

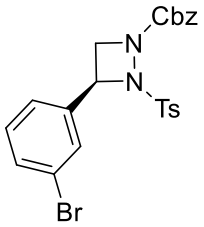


Benzyl (*S*)-3-(3,4-dichlorophenyl)-2-tosyl-1,2-diazetidine-1-carboxylate (270). Following general procedure 7, **260** (100 mg, 0.20 mmol, 1.0 equiv), triphenylphosphine (129 mg, 0.49 mmol, 2.5 equiv), diethyl azodicarboxylate (76 µL, 0.49 mmol, 2.5 equiv) and tetrahydrofuran (20 mL, 0.01 M) yielded **270** as a white solid (75 mg, 0.15 mmol, 78%). M.p. 133-135 °C; R_f = 0.23 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +33.2 (*c* 4.40, $CHCl_3$); Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 25.0 min; t_R 33.1 min; IR (film) 2983, 1711, 1337, 1313, 1212 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.86 (2H, d, *J* 7.6, Ar-H), 7.50-7.27 (8H, m, Ar-H), 7.19 (2H, d, *J* 8.5, Ar-H), 5.25-4.98 (3H, m, CHAr and CH_2Ph), 4.25 (1H, t, *J* 8.9, NC*H*H), 3.94 (1H, t, *J* 8.9, NCH*H*), 2.43 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 160.1 (C=O), 145.6 (Ar-C), 137.4 (Ar-C), 135.2 (Ar-C), 133.2 (Ar-C) 133.0 (Ar-C), 131.0 (Ar-CH), 130.2 (Ar-C) 130.0 (Ar-CH), 129.7 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.0 (Ar-CH), 125.6 (Ar-CH), 68.6 (CH_2), 60.0 (CH), 56.1 (CH_2), 21.8 (CH_3); HRMS (ESI^+) calculated for $C_{23}H_{20}{}^{35}Cl_2N_2O_5S$ $[M+Na]^+$ 513.0413; found 513.0413.

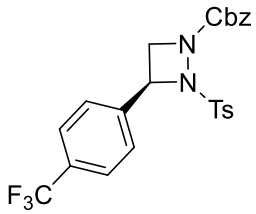


Benzyl (*R*)-3-(2-fluorophenyl)-2-tosyl-1,2-diazetidine-1-carboxylate (271). Following general procedure 7, **261** (44 mg, 0.10 mmol, 1.0 equiv), triphenylphosphine (36 mg, 0.15 mmol, 1.5 equiv), diethyl azodicarboxylate (22 µL, 0.15 mmol, 1.5 equiv) and tetrahydrofuran (10 mL, 0.01 M) yielded **271** as a colourless oil (32 mg, 70 µmol, 75%). R_f = 0.26 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ –15.6 (*c* 0.15, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 15.0 min; t_R 21.1 min; IR (film) 3034, 2924, 1720, 1236, 1162 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.83 (2H, d, *J* 8.2, Ar-H), 7.55 (1H, t, *J* 7.5, Ar-H), 7.30-7.26

(7H, m, Ar-H), 7.19 (1H, s, Ar-H), 7.10 (1H, t, *J* 7.5, Ar-H), 6.96 (1H, t, *J* 10.0, Ar-H), 5.20-5.04 (3H, m, CH_2Ph and NCHPh), 4.14 (1H, t, *J* 8.7, NC*H*H), 3.90 (1H, dd, *J* 8.4, 6.0, NCH*H*), 2.40 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 160.1 (C=O), 159.7 (d, *J* 246.3, Ar-CF), 145.5 (Ar-C), 135.4 (Ar-C), 130.4 (d, *J* 8.8, Ar-CH), 130.1 (Ar-CH), 130.0 (Ar-C), 129.7 (Ar-CH), 128.5 (Ar-CH), 128.5 (d, *J* 3.8, Ar-CH), 129.7 (Ar-CH), 128.3 (Ar-CH), 127.9 (Ar-CH), 124.7 (d, *J* 13.8, Ar-C), 124.7 (d, *J* 2.5, Ar-CH), 115.5 (d, *J* 20.0, Ar-CH), 68.4 (CH_2), 57.1 (d, *J* 3.8, CH), 56.1 (d, *J* 2.5, CH_2), 21.8 (CH_3); δ*F* (376 MHz; $CDCl_3$) -118.4 (CF); HRMS (ESI^+) calculated for $C_{23}H_{21}FN_2O_4S$ $[M+Na]^+$ 463.1098; found 463.1097.



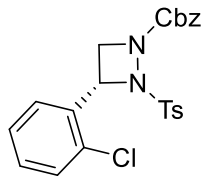
Benzyl (*S*)-3-(3-bromophenyl)-2-tosyl-1,2-diazetidine-1-carboxylate (274). Following general procedure 7, **264** (61 mg, 0.12 mmol, 1.0 equiv), triphenylphosphine (77 mg, 0.29 mmol, 2.5 equiv), diethyl azodicarboxylate (63 µL, 0.29 mmol, 2.5 equiv) and tetrahydrofuran (12 mL, 0.01 M) yielded **274** as a colourless oil (47 mg, 90 µmol, 79%). R_f = 0.25 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +34.8 (*c* 0.38, $CHCl_3$). Enantiomeric excess (97% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 9/91; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 19.6 min; t_R 25.1 min; IR (film) 2923, 1718, 1302, 1212 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.87 (2H, d, *J* 8.2, Ar-H), 7.50 (1H, s, Ar-H), 7.38-7.29 (8H, m, Ar-H), 7.23 (1H, t, *J* 7.8, Ar-H), 5.19 (1H, d, *J* 12.3 C*H*HAr), 5.11 (1H, d, *J* 12.3, CH*H*Ar), 5.07 (1H, dd, *J* 8.7, 6.0, NCHAr) 4.23 (1H, t, *J* 8.7, NC*H*H), 3.97 (1H, dd, *J* 8.7, 6.0, NCH*H*), 2.46 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 160.1 (C=O) 145.5 (Ar-C), 139.5 (Ar-C), 135.3 (Ar-C), 131.9 (Ar-CH), 130.6 (Ar-CH), 131.0 (Ar-CH), 130.3 (Ar-C) 130.0 (Ar-CH), 129.7 (Ar-CH), 129.4 (Ar-CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 127.9 (Ar-CH), 68.5 (CH_2), 60.5 (CH), 56.2 (CH_2), 21.8 (CH_3), 1 Ar-C and 1 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{23}H_{21}{}^{79}BrN_2O_4S$ $[M+Na]^+$ 523.0298; found 523.0294.



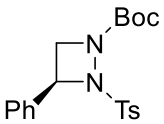
Benzyl (*S*)-2-tosyl-3-(4-(trifluoromethyl)phenyl)-1,2-diazetidine-1-carboxylate (275). Following general procedure 7, **265** (60 mg, 0.12 mmol, 1.0 equiv), triphenylphosphine (77 mg, 0.29 mmol, 2.5 equiv), diethyl azodicarboxylate (63 µL, 0.29 mmol, 2.5 equiv) and tetrahydrofuran (12 mL, 0.01 M) yielded **275** as a white solid (48 mg, 0.10 mmol, 82%). M.p. 117-119 °C; R_f = 0.21 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +18.9 (*c* 2.86, $CHCl_3$). Enantiomeric excess (94% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 19.5 min; t_R 24.3 min; IR (film) 2925, 1750, 1693, 1360, 1151, 1087 cm^{-1}; δ*H* (500 MHz; d6-DMSO) 7.89 (2H, d, *J* 8.2, Ar-H), 7.79 (2H, d, *J* 8.2, Ar-H) 7.65 (2H, d, *J* 8.1, Ar-H), 7.54 (2H, d, *J* 8.1, Ar-H), 7.39-7.32 (5H, m, Ar-H), 5.38-5.09 (3H, m, C*H*OH and CH_2Ph), 4.09 (1H, t, *J* 8.9, NC*H*H), 3.93 (1H, dd, *J* 8.9, 5.8, NCH*H*), 2.46 (3H, s, CH_3); δ*C* (125 MHz; d6-DMSO) 159.5 (C=O) 145.6 (Ar-C), 135.6 (Ar-C), 130.1 (Ar-CH), 129.8 (Ar-CH), 129.2 (Ar-C), 129.0 (q, *J* 31.9, Ar-C), 128.4 (Ar-CH), 128.2 (Ar-CH), 127.7 (Ar-CH), 127.4 (Ar-CH), 125.6 (q, *J* 3.8, Ar-CH), 124.1 (q, *J* 272.2, CF_3), 67.8 (CH_2), 60.1 (CH), 56.1 (CH_2), 21.3 (CH_3), 1 Ar-C not seen; δ*F* (376 MHz; d6-DMSO) -61.1 (CF_3); HRMS (ESI^+) calculated for $C_{24}H_{21}F_3N_2O_4S$ $[M+Na]^+$ 513.1066; found 513.1061.

Crystal Structure of **275.** Single crystals of $C_{24}H_{21}F_3N_2O_4S$ were grown from a 9:1 ratio of hexane and isopropyl alcohol. A suitable crystal was selected and mounted on a glass fibre with Fromblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a duel source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Crystal Data for $C_{24}H_{21}F_3N_2O_4S$ (M = 490.49 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 32.8358(3) Å, *b* = 11.60538(10) Å, *c* = 5.85758(7) Å, *V* = 2232.16(4) $Å^3$, *Z* = 4, T = 150(2) K, μ(CuKα) = 1.827 mm^{-1}, *Dcalc* = 1.460 g/cm^3, 72297 reflections measured (8.08° ≤ 2Θ ≤ 147.05°), 4499 unique (R_{int} = 0.0917, R_{sigma} = 0.0256) which were used in all calculations. The final R_1 was 0.0616 (I > 2σ(I)) and wR_2 was 0.1478 (all data). Data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1944267.

Flack x: 0.015(9) Shelx2018, Hooft y: 0.009(5) Olex2. Both the Flack parameter and associated Hooft y parameter are small, so confidence in the handedness of the chiral centre is high.

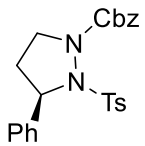


Benzyl (*R*)-3-(2-chlorophenyl)-2-tosyl-1,2-diazetidine-1-carboxylate (276). Following general procedure 7, **266** (81 mg, 0.17 mmol, 1.0 equiv), triphenylphosphine (112 mg, 0.43 mmol, 2.5 equiv), diethyl azodicarboxylate (66 µL, 0.43 mmol, 2.5 equiv) and tetrahydrofuran (17 mL, 0.01 M) yielded **276** as a colourless oil (50 mg, 0.11 mmol, 65%). R_f = 0.24 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +33.2 (*c* 0.44, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 13.6 min; t_R 17.1 min. IR (film) 2924, 1749, 1271, 1186 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.92 (2H, d, *J* 8.2, Ar-H), 7.83 (1H, d, *J* 7.0, Ar-H), 7.37-7.27 (9H, m, Ar-H), 5.25 (1H, dd, *J* 8.6, 5.9, CHAr), 5.21 (1H, d, *J* 12.4, C*H*HPh), 5.11 (1H, d, *J* 12.4, CH*H*Ph), 4.25 (1H, t, *J* 8.7, NC*H*H), 3.83 (1H, dd, *J* 8.6, 5.8, NCH*H*), 2.48 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 160.2 (C=O) 145.6 (Ar-C), 135.4 (Ar-C), 135.3 (Ar-C), 131.0 (Ar-C) 130.1 (Ar-CH), 130.0 (Ar-C), 129.8 (Ar-CH), 129.6 (Ar-CH), 129.2 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 127.5 (Ar-CH), 68.4 (CH_2), 59.8 (CH), 56.5 (CH_2), 21.8 (CH_3); HRMS (ESI^+) calculated for $C_{23}H_{21}{}^{35}ClN_2O_4S$ $[M+Na]^+$ 479.0803; found 479.0805.



***tert*-Butyl (*S*)-3-phenyl-2-tosyl-1,2-diazetidine-1-carboxylate (212)** Following general procedure 7, alcohol **211** (450 mg, 1.11 mmol, 1.0 equiv), triphenylphosphine (727 mg, 2.77 mmol, 2.5 equiv), diethylazodicarboxylate (436 µL, 2.77 mmol, 2.5 equiv) and tetrahydrofuran (111 mL, 0.01 M) yielded **212** as a white solid (328 mg, 0.84 mmol, 76%). R_f = 0.25 (15% EtOAc/petroleum ether); M.p. 166-167 °C; $[\alpha]_D^{28}$ +7.6 (*c* 0.09, $CHCl_3$); Enantiomeric excess (98% *ee*) was determined by HPLC

analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 0.6/99.4; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 54.5 min; t_R 63.1 min. IR (film) 2980, 2932, 1733, 1395, 1358 cm^{-1}; δ*H* (500 MHz, $CDCl_3$) 7.93 (2H, d, *J* 8.2, Ar-CH), 7.37 (7H, m, Ar-CH), 5.06 (1H, dd, *J* 8.7, 5.9, CHPh), 4.21 (1H, t, *J* 8.7, NC*H*H), 3.96 (1H, dd, *J* 8.5, 5.9, NCH*H*), 2.51 (3H, s, CH_3), 1.45 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz, $CDCl_3$) 159.3 (C=O), 145.2 (Ar-C), 137.6 (Ar-C), 130.8 (Ar-CH), 130.1 (Ar-CH), 130.0 (Ar-C), 129.6 (Ar-CH), 128.9 (Ar-CH), 126.4 (Ar-CH), 82.9 (C), 61.3 (CH), 56.3 (CH_2), 28.0 (CH_3), 21.8 (CH_3); HRMS (ES^+) calculated for $C_{20}H_{24}N_2O_4S$ $(M+Na)^+$ 411.1349; found 411.1352.

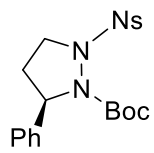


Benzyl (*R*)-3-phenyl-2-tosylpyrazolidine-1-carboxylate (309). Following general procedure 7, **298** (60 mg, 0.13 mmol, 1.0 equiv), triphenylphosphine (52 mg, 0.20 mmol, 1.5 equiv), diethylazodicarboxylate (31 µL, 0.20 mmol, 1.5 equiv) and tetrahydrofuran (13 mL, 0.01 M) yielded **309** as a white solid (51 mg, 0.12 mmol, 90%). M.p. 105-106 °C; R_f = 0.24 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ + 52.1 (*c* 0.02, $CHCl_3$). Enantiomeric excess (96% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 13.0 min; t_R 14.1 min. IR (film) 3034, 2959, 2925, 1702, 1344, 1216, 1181 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.84 (2H, d, *J* 8.2, Ar-CH), 7.37-7.31 (5H, m, Ar-H), 7.28-7.22 (5H, m, Ar-H), 7.21-7.18 (2H, m, Ar-H), 5.37 (1H, dd, *J* 8.0, 4.7, C*H*Ph), 5.09 (1H, d, *J* 12.2, CO_2CHHPh), 4.82 (1H, d, *J* 12.2, CO_2CHHPh), 3.98 (1H, ddd, *J* 11.0, 8.4, 5.7, NC*H*H), 3.29 (1H, dt, *J* 10.8, 8.3, NCH*H*), 2.45-2.39 (4H, m, CH_3 and CHPhC*H*H), 2.17 (1H, dtd, *J* 12.7, 7.2, 5.1, CHPhCH*H*); δ*C* (125 MHz; $CDCl_3$) 157.3 (C=O), 144.8 (Ar-C), 139.9 (Ar-C) 135.6 (Ar-C), 133.2 (Ar-C), 129.6 (Ar-CH), 129.4 (Ar-CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.6 (Ar-CH), 126.2 (Ar-CH), 68.2 (CH_2), 63.4 (CH), 47.8 (CH_2), 33.8 (CH_2), 21.7 (CH_3); HRMS (ESI^+) calculated for $C_{24}H_{24}N_2O_4S$ $[M+Na]^+$ 459.1349; found 459.1349.

Crystal Structure of **309.** Single crystals of $C_{24}H_{24}N_2O_4S$ were grown from a 9:1 mix of hexane and isopropyl alcohol. A suitable crystal was selected and

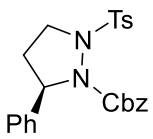
mounted on a Mitegen loop with Fomblin oil and placed on a Rigaku 007HF equipped with Varimax confocal mirrors and an AFC11 goniometer and HyPix 6000 detector. The crystal was kept at 100(2) K during data collection. Crystal Data for $C_{24}H_{24}N_2O_4S$ (M = 436.51 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 6.0985(4) Å, *b* = 11.5023(5) Å, *c* = 30.8387(15) Å, *V* = 2163.2(2) Å3, *Z* = 4, T = 100(2) K, μ(CuKα) = 1.610 mm^{-1}, *Dcalc* = 1.340 g/cm^3, 17168 reflections measured (5.732° ≤ 2Θ ≤ 136.448°), 3915 unique (R_{int} = 0.1033, R_{sigma} = 0.0835) which were used in all calculations. The final R_1 was 0.0624 (I > 2σ(I)) and *wR2* was 0.1773 (all data). Data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1944268.

Flack x: -0.03(3) Shelx2018, Hooft y: -0.05(2) Olex2. Both the Flack parameter and associated Hooft y parameter are small, so confidence in the handedness of the chiral centre is high.

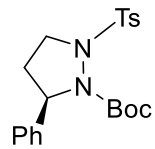


***tert*-Butyl (*R*)-5-(thiophen-2-yl)-2-tosylpyrazolidine-1-carboxylate (307).** Following general procedure 7, **296** (42 mg, 0.09 mmol, 1.0 equiv), triphenylphosphine (37 mg, 0.14 mmol, 1.5 equiv), diethylazodicarboxylate (22 μL, 0.14 mmol, 1.5 equiv) and tetrahydrofuran (9 mL, 0.01 M) yielded **307** as a colourless oil (36 mg, 0.08 mmol, 85%). R_f = 0.18 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ + 7.8 (*c* 0.17, $CHCl_3$). Enantiomeric excess (99% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 25.6 min; t_R 28.9 min. IR (film) 2979, 2931, 1712, 1530, 1346, 1161 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 8.27 (2H, d, *J* 8.6, Ar-H), 8.18 (2H, t, *J* 8.7, Ar-H) 7.43 (2H, d, *J* 6.9, Ar-H), 7.36 (2H, t, *J* 7.4, Ar-H), 7.31 (1H, d, *J* 7.1, Ar-H), 5.04 (1H, t, *J* 8.6, C*H*Ph), 4.21 (1H, br s, NC*H*H), 3.42 (1H, br s, NCH*H*), 2.59 (2H, dt, *J* 12.9, 6.5, CHPhC*H*H), 2.31 (1H, p, *J* 11.5, CHPhCH*H*), 1.27 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 155.8 (C=O seen on HMBC), 142.9 (Ar-C), 130.7 (Ar-CH), 128.4 (Ar-CH), 127.5 (Ar-CH), 126.6 (Ar-CH), 123.7 (Ar-CH), 114.1 (Ar-C), 82.7 (C), 65.4 (CH), 49.3 (CH_2), 36.1

(CH_2), 27.9 (CH_3), 1 Ar-C not seen; HRMS (ESI^+) calculated for $C_{20}H_{23}N_3O_6$ $[M+Na]^+$ 456.1200; found 456.1198.

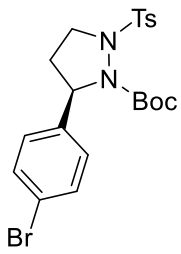


Benzyl (*R*)-5-phenyl-2-tosylpyrazolidine-1-carboxylate (306). Following general procedure 7, **295** (936 mg, 2.06 mmol, 1.00 equiv), triphenylphosphine (1.35 g, 5.15 mmol, 2.50 equiv), diethylazodicarboxylate (839 µL, 5.15 mmol, 2.50 equiv) and tetrahydrofuran (21 mL, 0.01 M) gave **306** as a white solid (803 mg, 1.84 mmol, 89%). R_f = 0.21 (25% EtOAc in petroleum ether). M.p. 122-123 °C $[\alpha]^{32}_D$ + 52.78 (c 0.04, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 5/95; flow rate = 1 mL/min; detection wavelength = 254 nm] t_R 17.5 min: t_R 19.7 min. IR (film) 3056, 2951, 2921, 1705, 1354, 1220, cm^{-1}; δH (500 MHz; $CDCl_3$) 7.76 (2H, d, *J* 8.0, Ar-CH), 7.48-7.42 (2H, m, Ar-H) 7.35-7.27 (6H, m, Ar-H), 7.17 (2H, s, Ar-H), 7.10 (2H, d, *J* 7.6, Ar-H), 5.13-5.00 (2H, m, CHPh and CH_2Ph 1 diastereotopic proton), 4.94 (1H, d, *J* 12.3, CH_2Ph), 4.15-4.05 (1H, m, NCH_2 1 diastereotopic proton), 3.29 (1H, br s, NCH_2 1 diastereotopic proton), 2.51 (1H, br s, CHPhCH_2 1 diastereotopic proton) 2.35-2.25 (4H, m, CH_3 and $CHPhCH_2$ 1 diastereotopic proton); δC (125 MHz; $CDCl_3$) 157.6 (C=O seen on HMBC), 144.7 (Ar-C), 140.6 (Ar-C) 135.6 (Ar-C), 133.6 (Ar-C), 129.4 (Ar-CH), 129.4 (Ar-CH), 128.4 (Ar-CH), 128.4 (Ar-CH) 128.1 (Ar-CH), 128.0 (Ar-CH), 127.4 (Ar-CH), 126.7 (Ar-CH), 68.3 (CH_2), 65.5 (CH), 49.5 (CH_2), 35.8 (CH_2), 21.7 (CH_3); HRMS (ESI^+) calculated for $C_{24}H_{24}N_2O_4S$ $[M+Na]^+$ 459.1349; found 459.1340.

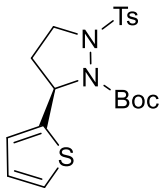


***tert*-Butyl (*R*)-5-phenyl-2-tosylpyrazolidine-1-carboxylate (308).** Following general procedure 7, **297** (72 mg, 0.17 mmol, 1.0 equiv), triphenylphosphine (112 mg, 0.43 mmol, 2.5 equiv), diethyl azodicarboxylate (74 mg, 0.43 mmol, 2.5 equiv) in tetrahydrofuran (17 mL, 0.01 M) yielded **308** as a colourless oil (62 mg, 0.15 mmol, 90%). R_f = 0.30 (30% EtOAc in petroleum ether); $[\alpha]^{32}_D$ + 23.5 (*c* 0.70, $CHCl_3$). Enantiomeric excess (95% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA

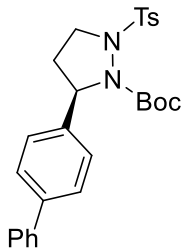
column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 10.9 min; t_R 17.4 min. IR (film) 2987, 2900, 1706, 1405, 1075 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.86-7.85 (2H, m, Ar-H), 7.45-7.25 (7H, m, Ar-H), 4.99 (1H, dd, *J* 8.7, 6.2, CHPh), 4.10 (1H, br s, NC*H*H), 3.29 (1H, br s, NCH*H*), 2.48-2.26 (5H, m, CH_2, CH_3), 1.25 (9H, s, $(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 156.6 (C=O), 144.7 (Ar-C), 141.5 (Ar-C), 133.8 (Ar-C), 129.6 (Ar-CH), 129.5 (Ar-CH), 128.4 (Ar-CH), 127.2 (Ar-CH), 126.8 (Ar-CH), 82.0 (C), 65.6 (CH), 49.3 (CH_2), 36.1 (CH_2), 27.9 (CH_3), 21.7 (CH_3); HRMS (ESI^+) calculated for $C_{21}H_{26}N_2NaO_4S$ $[M+Na]^+$ 425.1505; found 425.1504.



***tert*-Butyl (*R*)-5-(4-bromophenyl)-2-tosylpyrazolidine-1-carboxylate (310).** Following general procedure 7, **299** (61 mg, 0.12 mmol, 1.0 equiv), triphenylphosphine (47 mg, 0.18 mmol, 1.5 equiv), diethyl azodicarboxylate (28 µL, 0.18 mmol, 1.5 equiv) and tetrahydrofuran (12 mL, 0.01 M) yielded **310** as a colourless oil (52 mg, 0.11 mmol, 90%). R_f = 0.22 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +34.6 (*c* 0.25, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 5/95; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 12.5 min; t_R 15.5 min. IR (film) 2979, 2928, 1705, 1366, 1133 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.77 (2H, d, *J* 8.1, Ar-H), 7.39 (2H, d, *J* 8.4, Ar-H), 7.30 (2H, s, Ar-H), 7.19 (2H, d, *J* 7.8, Ar-H), 4.88 (1H, t, *J* 9.8 C*H*Ar), 4.07 (1H, br s, NC*H*H), 3.20 (1H, br s, NCH*H*), 2.43 (1H, sex, *J* 6.9, CHArC*H*H), 2.46 (3H, s, CH_3), 2.05-1.82 (1H, m, CHArCH*H*), 1.19 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 156.3 (C=O, seen on HMBC), 144.8 (Ar-C), 140.4 (Ar-C), 133.6 (Ar-C), 131.4 (Ar-CH), 129.6 (Ar-CH), 129.4 (Ar-CH), 128.6 (Ar-CH), 121.1 (Ar-C), 82.2 (C), 65.0 (CH), 49.3 (CH_2), 36.0 (CH_2), 27.9 (CH_3), 21.7 (CH_3); HRMS (ESI^+) calculated for $C_{21}H_{25}{}^{79}BrN_2O_4S$ $[M+Na]^+$ 503.0611; found 503.0612.

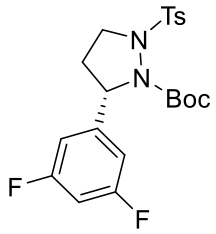


***tert*-Butyl (*R*)-5-(thiophen-2-yl)-2-tosylpyrazolidine-1-carboxylate (311).** Following general procedure 7, **300** (41 mg, 0.10 mmol, 1.0 equiv), triphenylphosphine (39 mg, 0.15 mmol, 1.5 equiv), diethylazodicarboxylate (24 µL, 0.15 mmol, 1.5 equiv) and tetrahydrofuran (10 mL, 0.01 M) yielded **311** as a colourless oil (28 mg, 0.07 mmol, 72%). R_f = 0.26 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +31.3 (*c* 0.07, $CHCl_3$). Enantiomeric excess (73% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 3/97; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 18.5 min; t_R 19.5 min. IR (film) 2978, 2925, 1704, 1256, 1133 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.79 (2H, d, *J* 7.9, Ar-H), 7.25 (1H, d, *J* 5.1, Ar-H), 7.23 (2H, d, *J* 7.9, Ar-H), 6.99 (1H, s, Ar-H), 6.94 (1H, t, *J* 3.7, Ar-H), 5.29 (1H, t, *J* 8.7, CHAr), 4.27 (1H, br s, NC*H*H), 3.32 (1H, br s, NCH*H*), 2.64-2.44 (2H, m, CHArCH_2), 2.42 (3H, s, CH_3), 1.32 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 156.3 (C=O seen on HMBC), 144.6 (Ar-C), 133.3 (Ar-C), 129.7 (Ar-CH), 129.3 (Ar-CH), 126.2 (Ar-CH), 125.1 (Ar-CH), 124.9 (Ar-CH), 82.3 (C), 60.7 (CH), 49.2 (CH_2), 35.5 (CH_2), 27.9 (CH_3), 21.6 (CH_3), 1 Ar-C not seen; HRMS (ESI^+) calculated for $C_{19}H_{24}N_2O_4S_2$ $[M+Na]^+$ 431.1070; found 431.1073.

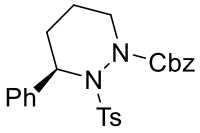


***tert*-Butyl (*R*)-5-([1,1'-biphenyl]-4-yl)-2-tosylpyrazolidine-1-carboxylate (312).** Following general procedure 7, **301** (84 mg, 0.17 mmol, 1.0 equiv), triphenylphosphine (66 mg, 0.25 mmol, 1.5 equiv), diethyl azodicarboxylate (39 µL, 0.25 mmol, 1.0 equiv) and tetrahydrofuran (17 mL, 0.01 M) yielded **312** as a white solid (70 mg, 0.15 mmol, 86%). M.p. 109-111 °C; R_f = 0.24 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +75.0 (*c* 0.03, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 9.5 min; t_R 10.5 min. IR (film) 2980, 2924, 1701, 1393, 1357, 1255 cm^{-1} δ*H* (500 MHz; $CDCl_3$) 7.90 (2H, d, *J* 8.2, Ar-H), 7.63 (4H, t, *J* 7.5, Ar-H), 7.60 (2H, d, *J* 7.9, Ar-H), 7.56 (2H, s, Ar-H), 7.47 (2H, t, *J* 7.6, Ar-H), 7.37 (1H, t, *J*

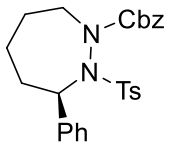
7.4, Ar-H), 7.27 (1H, d, *J* 9.4, Ar-H), 5.07 (1H, t, *J* 8.8, C*H*Ar), 4.17 (1H, br s, NC*H*H), 3.33 (1H, br s, NCH*H*), 2.58-2.49 (1H, m, CHArC*H*H), 2.46-2.35 (4H, m, CH_3 and CHNCH*H*), 1.30 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 156.8 (C=O seen on HMBC), 150.5 (Ar-C), 144.6 (Ar-C), 140.9 (Ar-C), 140.1 (Ar-C), 133.8 (Ar-C), 129.6 (Ar-CH), 129.4 (Ar-CH), 128.8 (Ar-CH), 127.2 (Ar-CH), 127.1 (Ar-CH), 82.1 (C), 65.3 (CH), 49.3 (CH_2), 36.0 (CH_2), 27.9 (CH_3) 21.6 (CH_3), 2 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{27}H_{30}N_2O_4S$ $[M+Na]^+$ 501.1818; found 501.1819.



***tert*-Butyl (*S*)-5-(3,5-difluorophenyl)-2-tosylpyrazolidine-1-carboxylate (313).** Following general procedure 7, alcohol **302** (239 mg, 0.50 mmol, 1.0 equiv), triphenylphosphine (330 mg, 1.26 mmol, 2.5 equiv), diethylazodicarboxylate (198 µL, 1.26 mmol, 2.5 equiv) and tetrahydrofuran (50 mL, 0.01 M) yielded **313** as a white solid (193 mg, 0.44 mmol, 88%). R_f = 0.08 (15% EtOAc in petroleum ether); $[\alpha]_D^{24}$ –16.4 (*c* 0.11, $CHCl_3$); Enantiomeric excess (93% *ee*) was determined by HPLC analysis (15 °C). [Chiralcel OD column 2-propanol/hexane = 1/99; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 34.7 min; t_R 43.2 min. M.p. 103-104 °C; IR (film) 2974, 1721, 1680, 1155, 1113 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.85 (2H, d, *J* 8.2, Ar-*H*), 7.28 (2H, d, *J* 8.1, Ar-H), 6.98 (2H, d, *J* 6.0, Ar-H), 6.70 (1H, tt, *J* 8.8, 2.2, Ar-H), 6.33 (1H, s, NH), 4.98 (1H, d, *J* 8.9, CHAr), 4.24-4.12 (1H, br m, C*H*HN), 3.33-3.21 (1H, br m, CH*H*N), 2.54-2.46 (1H, m, CHArC*H*H), 2.42 (3H, s, C*H*$_3$), 2.36-2.24 (1H, br m, CHArCH*H*), 1.27 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 162.9 (dd, *J* 246.3, 12.5, Ar-CF), 145.5 (Ar-C), 145.0 (Ar-C), 133.5 (Ar-C), 129.6 (Ar-CH), 129.5 (Ar-CH), 109.6 (d, *J* 25.0, Ar-CH), 102.6 (t, *J* 25.0, Ar-CH), 82.5 (C), 64.8 (CH), 49.2 (CH_2), 35.7 (CH_2), 27.8 (CH_3), 21.6 (CH_3), C=O not seen; δ*F* (376 MHz; $CDCl_3$) -109.7 (Ar-CF); HRMS (ESI^+) calculated for $C_{21}H_{24}N_2NaO_4SF_2$ $[M+Na]^+$ 461.1317; found 461.1322.



Benzyl (*R*)-3-phenyl-2-tosyltetrahydropyridazine-1(2H)-carboxylate (329). Following general procedure 4, **323** (46 mg, 0.10 mmol, 1.0 equiv), triphenylphosphine (39 mg, 0.15 mmol, 1.5 equiv), diethylazodicarboxylate (23 µL, 0.15 mmol, 1.5 equiv) and tetrahydrofuran (10 mL, 0.01 M) yielded **329** as a colourless oil (29 mg, 0.06 mmol, 63%). R_f = 0.29 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +43.8 (*c* 0.04, $CHCl_3$). Enantiomeric excess (94% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 1.5/98.5; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 34.0 min; t_R 36.3 min. IR (film) 2953, 2925, 1706, 1353, 1260 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.79-7.66 (2H, m, Ar-H), 7.60-7.31 (6H, m, Ar-H) 7.22-7.06 (6H, m, Ar-H), 5.21-5.08 (1H, m, C*H*Ph), 4.85 (1H, d, *J* 11.8, CO_2CHH), 4.70 (1H, d, *J* 11.9, CO_2CHH), 4.28-4.02 (1H, m, NC*H*H), 3.71-3.44 (1H, m, NCH*H*), 2.43-2.31 (4H, m, CH_3 and CHPhC*H*H), 2.17-2.10 (1H, m, CHPhCH*H*), 1.97 (1H, br s, CH_2CHHCH_2), 1.78-1.71 (1H, m, CH_2CHHCH_2); δ*C* (125 MHz; $CDCl_3$) 155.9 (C=O), 144.4 (Ar-C), 138.6 (Ar-C) 135.5 (Ar-C), 134.9 (Ar-C), 132.2 (Ar-CH), 132.0 (Ar-CH), 129.4 (Ar-CH), 128.8 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.2 (Ar-CH), 127.4 (Ar-CH), 68.2 (CH_2), 57.4 (CH), 43.6 (CH_2), 29.7 (CH_2), 21.7 (CH_3), 19.1 (CH_2); HRMS (ESI^+) calculated for $C_{25}H_{26}N_2O_4S$ $[M+Na]^+$ 473.1505; found 473.1503.



Benzyl (*R*)-3-phenyl-2-tosyl-1,2-diazepane-1-carboxylate (330). Following general procedure 7, **324** (27 mg, 56 µmol, 1.0 equiv), triphenylphosphine (22 mg, 84 µmol, 1.5 equiv), diethylazodicarboxylate (13 µL, 84 µmol, 1.5 equiv) and tetrahydrofuran (5.6 mL, 0.01 M) yielded **330** as a colourless oil (17 mg, 38 µmol, 67%). R_f = 0.31 (25% EtOAc in petroleum ether); $[\alpha]^{32}_D$ +22.3 (*c* 0.09, $CHCl_3$). Enantiomeric excess (90% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak OD-H column 2-propanol/hexane = 2/98; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 14.8 min; t_R16.8 min. IR (film) 2925, 2856, 1705, 1401, 1126 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.34-7.23 (5H, m, Ar-CH), 7.15-7.00 (6H, m,

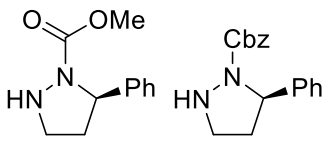
Ar-H) 6.90-6.84 (3H, m, Ar-H), 5.11-5.00 (1H, m, CHPh), 4.85 (1H, d, *J* 11.8, CO_2CHHPh), 4.70 (1H, d, *J* 11.9, CO_2CHHPh), 4.28-4.02 (1H, m, NC*H*H), 3.71-3.44 (1H, m, NCH*H*), 2.43-2.31 (4H, m, CH_3 and CHPhC*H*H) 2.17-2.10 (1H, m, CHPhCH*H*), 1.99-1.72 (4H, br s, $CH_2(CH_2)_2CH2$),; δ*C* (125 MHz; $CDCl_3$) 156.2 (minor rotamer) and 156.1 (C=O), 143.5 (Ar-C) and 143.4 (minor rotamer), 142.6 (Ar-C) and 142.3 (minor rotamer), 136.3 (minor rotamer) and 136.2 (Ar-C), 136.1 (minor rotamer) and 135.0 (Ar-C), 129.1 (Ar-CH), 128.9 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 127.5 (Ar-CH), 127.2 (Ar-CH), 127.0 (Ar-CH), 126.9 (Ar-CH), 68.5 (minor rotamer) and 67.0 (CH_2), 68.4 (CH), 54.1 (minor rotamer) and 52.9 (CH_2), 36.2 (minor rotamer) and 36.1 (CH_2), 28.3 (CH_2) and 28.2 (minor rotamer), 27.2 (minor rotamer) and 26.3 (CH_2), 21.5 (CH_3); HRMS (ESI^+) calculated for $C_{26}H_{28}N_2O_4S$ $[M+Na]^+$ 487.1662; found 487.1656.

Yoshida's Explosion Propagation Correlation Raw Data

The exotherm data was taken directly from the DSC traces and used without modification. The DSC data was generated using a Mettler Toledo DSC 3 Calorimeter equipped with an FRS 5+ sensor. The compounds were weighed into a gold crucible and sealed, and all samples were measured against an empty plate as a reference. They were analysed from 40-450 °C and heated at a rate of 10 °C per minute. Each sample was analysed twice and the average of each exotherm energy and initiation temperature was used to generate the plot, the error bars were from the two values. This gave the raw data that was subsequently used to generate Figure 2.3 (Table 6.1).

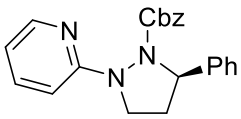
Compound	Heat of Decomp /J g^{-1}	Exotherm / °C	log Q_{DSC}/ cal g^{-1}	log (T_{DSC}-25)/ °C	EP	Error Bar
1 Max	**932**	**130**	2.35	2.02	-0.09	2.35
1 Min	**818**	**130**	2.29	2.02	-0.15	-2.29
2 Max	**593**	**170**	2.15	2.16	-0.34	2.15
2 Min	**563**	**170**	2.13	2.16	-0.36	-2.13
3 Max	**584**	**160**	2.14	2.13	-0.34	2.14
3 Min	**464**	**190**	2.04	2.22	-0.47	-2.04
4 Max	**437**	**180**	2.02	2.19	-0.48	2.02
4 Min	**308**	**180**	1.87	2.19	-0.64	-1.87
5 Max	**370**	**180**	1.95	2.19	-0.56	1.95
5 Min	**281**	**180**	1.83	2.19	-0.68	-1.83
6 Max	**284**	**200**	1.83	2.24	-0.69	1.83
6 Min	**276**	**200**	1.82	2.24	-0.70	-1.82
7 Max	**348**	**185**	1.92	2.20	-0.59	1.92
7 Min	**240**	**185**	1.76	2.20	-0.75	-1.76

Table 6.1 Raw data used to plot Yoshida's explosion propagation correlation

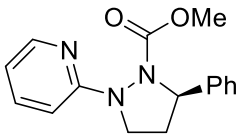


methyl (*R*)-5-phenylpyrazolidine-1-carboxylate (350) and **benzyl (R)-5-phenylpyrazolidine-1-carboxylate (349) 306** (200 mg, 0.46 mmol 1.0 equiv), activated magnesium turnings (56 mg, 2.29 mmol, 5.0 equiv) and MeOH (5 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a colourless oil. This contained a mixture of **349** and **350**, these were separated using prep HPLC: The residue was taken up in MeOH (to a total volume of 9.8 ml), filtered and purified by prep-HPLC (Phenomenex Gemini-NX 10 Micron 50*150mm

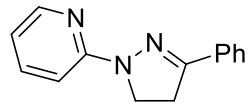
C-18) (CH_3CN & Water with 10 mM ammonium bicarbonate adjusted to pH 9 with ammonium hydroxide, 30 % to 100% CH3CN over 11 minutes at 120ml/min) (1 injection) (220 nm). They were used directly in the synthesis of **351** and **352** without further purification or characterisation.



Benzyl (*R*)-5-phenyl-2-(pyridin-2-yl)pyrazolidine-1-carboxylate (351). 349 (77 mg, 0.28 mmol, 1.0 equiv), palladium dibenzylacetone (18.9 mg, 0.021 mmol, 0.075 equiv), 1,1′-Ferrocenediyl-bis(diphenylphosphine) (33.5 mg, 0.061 mmol, 0.22 equiv), cesium carbonate (108.0 mg, 0.33 mmol, 1.2 equiv) and 2-bromopyridine (27.6 µL, 0.29 mmol, 1.05 equiv) in toluene (0.92 mL, 0.3 M) were heated to 90 °C and stirred for 20 h. The solution was then quenched with saturated ammonium chloride solution (5 mL), extracted with dichloromethane (3 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. This was purified by flash chromatography (10% to 60% EtOAc/hexane) to yield **351** as a white solid (40 mg, 0.11 mmol, 41%). R_f = 0.11 (10% EtOAc/hexane); M. P. 108-110 °C $[\alpha]^{32}_D$ – 68.8 (c 0.03, CH_2Cl_2). IR (film) 2924, 1721, 1342, 1121 cm^{-1}; δH (400 MHz; CH_2Cl_2) 8.25 (1H, d, *J* 3.8, Ar-H), 7.53 (1H, td, *J* 8.0 and 2.0, Ar-H), 7.30-7.15 (10H, m, Ar-*H*), 6.93 (1H, d, *J* 8.4 Ar-H), 6.82 (1H, dd, *J* 7.0 and 5.1, Ar-H), 5.27-5.14 (3H, m, C*H*Ph and CH_2Ph), 4.96-4.90 (1H, m, NCHH), 3.40 (1H, td, *J* 11.1 and 6.0, NCHH), 2.55 (1H, dddd, *J* 13.7, 7.9, 6.1, 2.2, CHPhC*H*$_2$), 2.11-1.97 (1H, m, CHPhCHH); δC (100 MHz; $CDCl_3$) 160.8 (Ar-C) 158.0 (C=O), 147.5 (Ar-CH), 141.4 (Ar-C), 137.5 (Ar-CH), 136.1 (Ar-C), 128.5 (Ar-CH), 128.4 (Ar-CH), 127.8 (Ar-CH), 127.4 (Ar-CH), 126.8 (Ar-CH), 116.3 (Ar-CH), 110.6 (Ar-CH), 67.9 (CH), 64.8 (CH_2), 48.6 (CH_2), 36.0 (CH_2); HRMS (ESI^+) calculated for $C_{22}H_{21}N_3O_2$ $[M+H]^+$ 360.1712; found 360.1712.



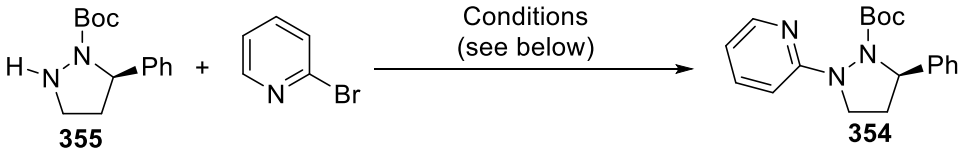
Methyl (*R*)-5-phenyl-2-(pyridin-2-yl)pyrazolidine-1-carboxylate (352). 350 (82 mg, 0.40 mmol, 1.0 equiv), palladium dibenzylacetone (27 mg, 30 µmol, 0.075 equiv), 1,1′-Ferrocenediyl-bis(diphenylphosphine) (49 mg, 87 µmol, 0.22 equiv), cesium carbonate (155 mg, 0.48 mmol, 1.2 equiv) and 2-bromopyridine (40 µL, 0.42 mmol, 1.05 equiv) in toluene (1.3 mL, 0.3 M) were heated to 90 °C and stirred for 20 h. The solution was then quenched with saturated ammonium chloride solution (5 mL), extracted with dichloromethane (3 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. This was purified by flash chromatography (10% to 60% EtOAc/hexane) to yield **352** as a white solid (58 mg, 0.20 mmol, 51%). R_f = 0.19 (25% ethyl acetate in petroleum ether); M. p. 102-104 °C; $[\alpha]^{32}_D$ – 92.1 (*c* 0.16, CH_2Cl_2). IR (film) 2924, 1717, 1426, 1344, 1201 cm^{-1}; δH (400 MHz; $CDCl_3$) 8.25 (1H, dd, *J* 4.9, 1.1, Ar-H), 7.56 (1H, td, *J* 8.0, 2.0, Ar-H), 7.32-7.17 (5H, m, Ar-*H*), 6.96 (1H, d, *J* 8.4 Ar-H), 6.83 (1H, ddd, *J* 7.2, 4.9, 0.7, Ar-H), 5.25 (1H, t, *J* 8.2, C*H*Ph), 4.92 (1H, ddd, *J* 11.1, 7.0, 1.8, NC*H*H), 3.78 (3H, s, OCH_3), 3.39 (1H, td, *J* 11.1, 6.0, NCH*H*), 2.57 (1H, dddd, *J* 12.7, 8.0, 6.0, 2.3, CHPhC*H*H), 2.07 (1H, dddd, *J* 12.7, 8.0, 6.0, 2.3, CHPhCH*H*); δ*C* (100 MHz; $CDCl_3$) 160.8 (Ar-C) 158.9 (C=O), 147.5 (Ar-CH), 141.3 (Ar-C), 137.6 (Ar-CH), 128.5 (Ar-CH), 127.4 (Ar-CH), 126.8 (Ar-CH), 116.4 (Ar-CH), 110.6 (Ar-CH), 64.7 (CH), 53.6 (CH_3), 48.7 (CH_2), 35.8 (CH_2); HRMS (ESI^+) calculated for $C_{16}H_{17}N_3O_2$ $[M+H]^+$ 284.1399; found 284.1400.



2-(3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)pyridine 353 351 (10 mg, 28 µmol, 1.0 equiv), palladium on charcoal (10 mg, 100 wt%), and ethanol (10 mL) were shaken in a parr hydrogenator for 21 h. The resulting solution was filtered through a plug of celite and concentrated in vacuo to give a white solid (7 mg, 28 µmol, quant.). Alternatively, **354** (35.0 mg, 0.11 mmol, 1.0 equiv), trifluoroacetic acid (1 mL) and dichloromethane (2 mL) were combined and stirred at rt for 1 h. The reaction was quenched with saturated sodium hydrogen carbonate (5 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried

over magnesium sulphate and concentrated in vacuo to yield **351** as a white solid (19.9 mg, 0.90 µmol, 83%). R_f = 0.21 (10% EtOAc in petroleum ether). M. p. 68-69 °C. IR (film) 2851, 1672, 2980, 1586, 1502, 1468, 1348, 1250 cm^{-1}; δH (500 MHz; $CDCl_3$); 8.13 (1H, d, *J* 4.9, Ar-CH), 7.69 (2H, d, *J* 7.3, Ar-CH), 7.51-7.45 (1H, m, Ar-CH), 7.40-7.27 (4H, m, Ar-CH), 6.65-6.61 (1H, m, Ar-CH), 4.10 (2H, t, *J* 10.5 CH_2), 3.21 (2H, t, *J* 10.5, CH_2); δC (125 MHz; $CDCl_3$) 156.3 (Ar-C), 151.5 (Ar-C), 147.5 (Ar-CH), 137.2 (Ar-CH), 132.6 (C), 129.0 (Ar-CH), 128.6 (Ar-CH), 125.9 (Ar-CH), 114.3 (Ar-CH), 109.3 (Ar-CH), 46.5 (CH_2), 31.7 (CH_2); HRMS (ESI^+) calculated for $C_{14}H_{14}N_3$ $[M+Na]^+$ 224.1182; found 224.1183.

<u>Buchwald-Hartwig Amination Screen 1 – 96 Well Screen</u>



Scheme 6.5 Buchwald-Hartwig Amination Screen 1.

The reactions were performed in an aluminium heating block with 96 x 750 µL vials, each with a teflon coated magnetic stirrer bar. These vials were arranged in 12 columns (labelled 1-12) and 8 rows (labelled A-H). The following powders were weighed into the vials using a Mettler Toledo QX96 powder dispenser inside a glovebox.

All vials in rows A, E: Sodium *tert*-butoxide (4.3 mg, 44 µmol, 2.0 equiv).

All vials in rows B, F: Caesium carbonate (14.4 mg, 44 µmol, 2.0 equiv).

All vials in rows C, G: Potassium carbonate (6.1 mg, 44 µmol, 2.0 equiv).

All vials in rows D, H: Potassium phosphate tribasic (9.4 mg, 44 µmol, 2.0 equiv).

All vials in column 1: [XantPhos Pd(allyl)]Cl (1.7 mg, 2.2 µmol, 0.1 equiv).

All vials in column 2: [(*R*)-BINAP Pd(allyl)]Cl (1.9 mg, 2.2 µmol, 0.1 equiv).

All vials in column 3: $Pd(dppf)Cl_2$ · dichloromethane (1.8 mg, 2.2 µmol, 0.1 equiv).

All vials in column 4: [P(*t*Bu)$_3$] Pd(crotyl) Cl (0.9 mg, 2.2 µmol, 0.1 equiv).

All vials in column 5: JohnPhos (0.8 mg, 2.2 µmol, 0.1 equiv) and palladium (II) acetate (0.5 mg, 2.2 µmol, 1.0 equiv).

All vials in column 6: AdBrettPhos (1.7 mg, 2.7 µmol, 0.12 equiv) and palladium (II) acetate (0.5 mg, 2.2 µmol, 0.1 equiv).

All vials in column 7: [*t*BuBrettPhos Pd(allyl)]OTf (1.7 mg, 2.2 µmol, 0.1 equiv).

All vials in column 8: MorDalPhos (1.2 mg, 2.6 µmol, 0.12 equiv) and palladium (II) acetate (0.5 mg, 2.2 µmol, 0.1 equiv).

All vials in column 9: [BrettPhos Pd(crotyl)]OTf (1.9 mg, 2.2 µmol, 0.1 equiv).

All vials in column 10: [*t*BuXPhos Pd(allyl)]OTf (1.6 mg, 2.2 µmol, 0.1 equiv).

All vials in column 11: XPhos Pd(crotyl)Cl (1.5 mg, 2.2 µmol, 0.1 equiv).

All vials in column 12: RuPhos Pd(crotyl)Cl (1.5 mg, 2.2 µmol, 0.1 equiv).

The following stock solutions were then made:

Stock Solution 1: *tert*-butyl (*R*)-5-phenylpyrazolidine-1-carboxylate (**355**) (286 mg, 1.15 mmol) and 2-bromopyridine (333 mg, 2.10 mmol) in toluene (4.42 mL).

Stock Solution 2: *tert*-butyl (*R*)-5-phenylpyrazolidine-1-carboxylate (**355**) (286 mg, 1.15 mmol) and 2-bromopyridine (333 mg, 2.10 mmol) in dioxane (4.42 mL).

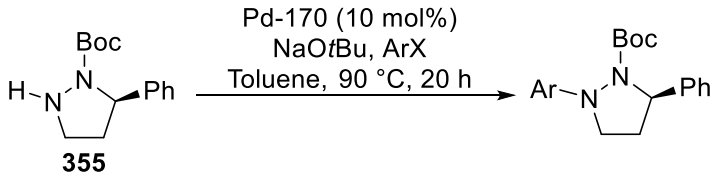
All vials in rows A-D were dosed with 85 µL of Stock Solution 1 which contained *tert*-butyl (*R*)-5-phenylpyrazolidine-1-carboxylate (**355**) (5.5 mg, 22 µmol, 1.0 equiv, obtained by deprotection of **308** using procedure in general method 5) and 2-bromopyridine (6.4 mg, 41 µmol, 1.8 equiv).

All vials in rows E-H were dosed with 85 µL of Stock Solution 2 which contained *tert*-butyl (*R*)-5-phenylpyrazolidine-1-carboxylate (**355**) (5.5 mg, 2.2 µmol, 1.0 equiv) and 2-bromopyridine (6.4 mg, 41 µmol, 1.8 equiv).

The plate was sealed with a silicone and PFA mat and placed on an HEL polyblock. The plate was then heated at 90 °C for 16 h. The vials were then cooled to rt and DMSO (300 µL) was added to each using a multichannel pipette. A 5 µL aliquot was extracted from each then added to a 96-well analyical plate and diluted with DMSO (50 µL). The plate was analyzed by reverse phase LCMS (XBridge C_{18} 3.5-µm 2.1 × 35 mm Column, 1.6 mL min^{-1}, 50 °C; gradient

5:95 to 99:1 (pH 9 H_2O + 10 mM NH_4HCO_2) / MeCN over 0.7 min + 0.3 min hold). The LCMS traces were processed using in-house software and the results visualized using Spotfire software to give Figure 3.1.

Buchwald-Hartwig Amination Screen 2 – 24 Well Halide Screen



Scheme 6.7 Buchwald-Hartwig Amination screen 2.

The reactions were performed in an aluminium heating block with 96 x 750 µL vials, each with a teflon coated magnetic stirrer bar. These vials were arranged in 12 columns (labelled 1-12) and 8 rows (labelled A-H). The following powders were weighed into the vials using a Mettler Toledo QX96 powder dispenser inside a glovebox.

Vials in rows A-D (columns 1-6 only): Sodium *tert*-butoxide (4.3 mg, 44 µmol, 2.0 equiv).

Vials in rows A-D (columns 1-6 only): XPhos Pd(crotyl)Cl (1.5 mg, 2.2 µmol, 0.1 equiv).

Vial A03: 4-Bromo-*N*,*N*-dimethylaniline (8.8 mg, 44 µmol, 2.0 equiv).

Vial B01: 2-Bromobenzonitrile (8.0 mg, 44 µmol, 2.0 equiv).

Vial B02: 3-Bromobenzonitrile (8.0 mg, 44 µmol, 2.0 equiv).

Vial B03: 4-Bromobenzenethiol (8.4 mg, 44 µmol, 2.0 equiv).

Vial B04: 2-Bromo-4-fluorophenol (8.4 mg, 44 µmol, 2.0 equiv).

Vial B05: 4-Bromo-3-nitroanisole (10.3 mg, 44 µmol, 2.0 equiv).

Vial B06: 5-Bromo-1-methylindole (9.3 mg, 44 µmol, 2.0 equiv).

Vial C01: 5-Bromo-1H-benzotriazole (8.8 mg, 44 µmol, 2.0 equiv).

Vial C02: 6-Bromobenzo[d]oxazole (8.8 mg, 44 µmol, 2.0 equiv).

Vial C03: 3-Bromophenyl Methyl Sulfone (10.4 mg, 44 µmol, 2.0 equiv).

Vial C04: 2-Bromo-N,N-dimethylbenzenesulfonamide (11.7 mg, 44 µmol, 2.0 equiv).

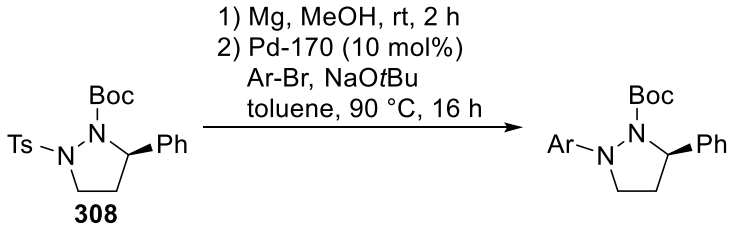
Vial C05: 6-Bromo-2,3-dihydrobenzofuran (8.8 mg, 44 µmol, 2.0 equiv).
Vial D04: 5-bromopyrimidine (7.0 mg, 44 µmol, 2.0 equiv).
Vial D05: 2-chloropyrimidine (5.1 mg, 44 µmol, 2.0 equiv).
All vials in rows A-D (columns 1-6 only) were dosed with 45 µL of Stock Solution 1 which contained *tert*-butyl (*R*)-5-phenylpyrazolidine-1-carboxylate (**355**) (5.5 mg, 2.2 µmol, 1.0 equiv).
Vials A03, B01-B06, C01-C05, D04 and D05 were dosed with 40 µL toluene.
Vial A01 was dosed with stock solution 2 which contained 40 µL toluene and bromobenzene (4.7 µL, 44 µmol, 2.0 equiv).
Vial A02 was dosed with stock solution 3 which contained 40 µL toluene and 4-bromo-1,2-dimethylbenzene (6.0 µL, 44 µmol, 2.0 equiv).
Vial A04 was dosed with stock solution 4 which contained 40 µL toluene and 1-bromo-3-fluorobenzene (4.9 µL, 44 µmol, 2.0 equiv).
Vial A05 was dosed with stock solution 5 which contained 40 µL toluene and 1-bromo-2,4-difluorobenzene (5.0 µL, 44 µmol, 2.0 equiv).
Vial A06 was dosed with stock solution 6 which contained 40 µL toluene and 3-bromobenzotrifluoride (6.2 µL, 44 µmol, 2.0 equiv).
Vial C06 was dosed with stock solution 7 which contained 40 µL toluene and 1-bromo-3-propylbenzene (6.7 µL, 44 µmol, 2.0 equiv).
Vial D01 was dosed with stock solution 8 which contained 40 µL toluene and 1-bromo-4-*tert*-butylbenzene (7.7 µL, 44 µmol, 2.0 equiv).
Vial D02 was dosed with stock solution 9 which contained 40 µL toluene and 1-bromo-4-methoxybenzene (5.5 µL, 44 µmol, 2.0 equiv).
Vial D03 was dosed with stock solution 10 which contained 40 µL toluene and 3-bromothiophene (4.1 µL, 44 µmol, 2.0 equiv).
Vial D06 was dosed with stock solution 11 which contained 40 µL toluene and 4-chlorotoluene (5.2 µL, 44 µmol, 2.0 equiv).
The plate was sealed with a silicone and PFA mat and placed on an HEL polyblock. The plate was then heated at 90 °C for 16 h. The vials were then cooled to rt and DMSO (300 µL) was added to each using a multichannel pipette. A 5 µL aliquot was extracted from each then added to a 96-well analyical plate and diluted with DMSO (50 µL). The plate was analyzed by reverse phase

LCMS (XBridge C_{18} 3.5-µm 2.1 × 35 mm Column, 1.6 mL min^{-1}, 50 °C; gradient 5:95 to 99:1 (pH 9 H_2O + 10 mM NH_4HCO_2) / MeCN over 0.7 min + 0.3 min hold). All 24 halides were analysed using the same methodology so their peaks could be ignored in the purity analysis. The LCMS traces were processed using in-house software and the results visualized using ChemDraw to give Figure 3.2. The raw data is given below (Table 6.2)

Vial	Ret Halide / min	Ret Product / min	LCMS Purity
A01	0.51	0.61	68%
A02	0.60	0.66	62%
A03	0.56	0.60	50%
A04	0.52	0.62	73%
A05	0.52	0.42	66%
A06	0.58	0.66	77%
B01	0.42	0.59	50%
B02	0.45	0.59	56%
B03	0.21/0.75	N/A	0% (SM)
B04	0.38	N/A	0% (SM)
B05	0.49	0.62	40%
B06	0.55	0.60	56%
C01	0.26/0.42	N/A	42% (SM)
C02	0.26	0.57	21% (SM)
C03	0.36	0.66	12%
C04	0.42	N/A	0%
C05	0.49	0.60	53%
C06	0.49	0.69	71%
D01	0.67	0.70	62%
D02	0.51	0.59	80%
D03	0.47	0.59	43%
D04	0.20	0.46	86%
D05	0.15	0.51	66%
D06	0.55	0.64	76%

Table 6.2 LCMS Purity of the products of the halide screen.

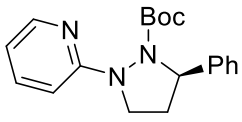
General procedure 8: Buchwald-Hartwig Amination



Scheme 6.8 General procedure for the Buchwald-Hartwig Amination

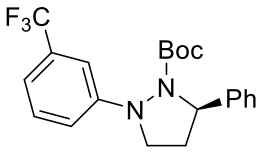
N.B. Magnesium turnings were activated by washing them with 1 M hydrochloric acid solution (2 × 20 mL), water (20 mL) and methanol (20 mL).

tert-Butyl-(*R*)-5-phenyl-2-tosylpyrazolidine-1-carboxylate (**308**) (1.0 equiv), activated magnesium turnings (5.0 equiv) and MeOH (0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a colourless oil. To this was added toluene (1.0 M) was added XPhos Pd(crotyl)Cl (0.1 equiv), sodium *tert*-butoxide (2.0 equiv) and aryl halide (2.0 equiv). The reaction mixture was stirred at 90 °C for 16 h. The mixture was cooled to rt then quenched with saturated ammonium chloride solution (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography (30% ethyl acetate in petroleum ether) to give the following compounds.



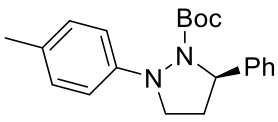
***tert*-Butyl (*R*)-5-phenyl-2-(pyridin-2-yl)pyrazolidine-1-carboxylate (354).** Following general procedure 8, **308** (72 mg, 0.18 mmol, 1.0 equiv), magnesium turnings (22 mg, 0.90 mmol, 5.0 equiv) and methanol (1.8 mL, 0.1 M), then XPhos Pd(crotyl)Cl (12 mg, 18 µmol, 0.1 equiv), sodium *tert*-butoxide (35 mg, 0.36 mmol, 2.0 equiv) and 2-bromopyridine (34 µL, 0.36 mmol, 2.0 equiv) in toluene (0.18 mL,

1.0 M) yielded **354** as a white solid (50 mg, 0.16 mmol, 85%). M.p. 98-99 °C; R_f = 0.34 (30% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ –91.3 (*c* 0.04, $CHCl_3$); IR (film) 2989, 1698, 1588, 1388, 1161 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 8.25 (1H, d, *J* 4.8, Ar-H), 7.59 (1H, td, *J* 7.8, 1.8, Ar-H), 7.30-7.18 (5H, m, Ar-H), 6.95 (1H, d, *J* 8.4, Ar-H), 6.82 (1H, dd, *J* 6.7, 5.3, Ar-H), 5.19 (1H, t, *J* 8.1, C*H*Ph), 4.89 (1H, t, *J* 10.3, NC*H*H), 3.49-3.41 (1H, m, NCH*H*), 2.58-2.51 (1H, m, CHPhC*H*H), 2.09-1.98 (1H, m, CHPhCH*H*), 1.43 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 160.9 (Ar-C), 156.8 (C=O), 147.3 (Ar-CH), 142.1 (Ar-C), 137.5 (Ar-CH), 128.4 (Ar-CH), 127.2 (Ar-CH), 126.6 (Ar-CH), 115.8 (Ar-CH), 110.4 (Ar-CH), 81.5 (C), 65.5 (CH), 48.2 (CH_2), 36.2 (CH_2), 28.2 (CH_3); HRMS (ESI^+) calculated for $C_{19}H_{24}N_3O_2$ $[M+Na]^+$ 326.1863; found 326.1867.

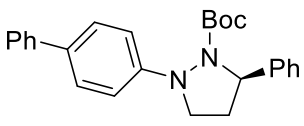


***tert*-Butyl (*R*)-5-phenyl-2-(3-(trifluoromethyl)phenyl)pyrazolidine-1-carboxylate (360).** Following general procedure 8, **308** (85 mg, 0.21 mmol, 1.0 equiv), magnesium turnings (26 mg, 1.05 mmol, 5.0 equiv) and methanol (2.1 mL, 0.1 M), then XPhos Pd(crotyl)Cl (7 mg, 10 µmol, 0.05 equiv), sodium *tert*-butoxide (40 mg, 0.42 mmol, 2.0 equiv) and 3-bromobenzotrifluoride (55 µL, 0.42 mmol, 2.0 equiv) in toluene (0.21 mL, 1.0 M) yielded **360** as a colourless oil (69 mg, 0.18 mmol, 85%). R_f = 0.28 (20% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ –9.8 (*c* 0.25, dichloromethane). IR (film) 2978, 2930, 1704, 1451, 1367, 1164 cm^{-1}; δH (500 MHz; $CDCl_3$7.37 (1H, t, *J* 8.0, Ar-CH), 7.30-7.21 (5H, m, Ar-H), 7.19 (1H, s, Ar-H), 7.15 (1H, d, *J* 7.6, Ar-H), 7.11 (1H, dd, *J* 8.3, 1.6, Ar-CH), 5.20 (1H, t, *J* 7.5, C*H*Ph), 3.85 (1H, ddd, *J* 11.0, 6.5, 4.5, NC*H*H), 3.69 (1H, ddd, *J* 11.0, 8.9, 6.3, NCH*H*), 2.54 (1H, qd, *J* 6.3, 4.5, CHPhC*H*H), 2.13 (1H, dt, *J* 15.7, 7.2, CHPhCH*H*), 1.39 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 156.1 (C=O), 150.7 (Ar-C), 141.4 (Ar-C), 131.1 (q, *J* 32.5, Ar-C), 129.3 (Ar-CH), 128.5 (Ar-CH), 127.4 (Ar-CH), 126.7 (Ar-CH), 124.3 (q, *J* 271.3, CF_3), 118.2 (Ar-CH), 117.9 (q, *J* 3.8, Ar-CH), 111.9 (q, *J* 3.8, Ar-CH), 81.7 (C), 63.3 (CH), 52.3 (CH_2), 35.4 (CH_2), 28.1 (CH_3); δ*F*

(282 MHz; $CDCl_3$) -62.8 (CF_3); HRMS (ESI^+) calculated for $F_3C_{21}H_{23}N_2O_2$ $[M+Na]^+$ 415.1604; found 415.1597.

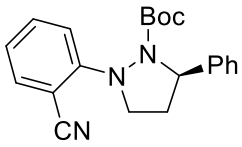


***tert*-Butyl (*R*)-5-phenyl-2-(*p*-tolyl)pyrazolidine-1-carboxylate (357).** Following general procedure 8, **308** (105 mg, 0.26 mmol, 1.0 equiv), magnesium turnings (32 mg, 1.30 mmol, 5.0 equiv) and methanol (2.6 mL, 0.1 M), then XPhos Pd(crotyl)Cl (18 mg, 26 µmol, 0.1 equiv), sodium *tert*-butoxide (50 mg, 0.52 mmol, 2.0 equiv) and 4-chlorotoluene (63 µL, 0.52 mmol, 2.0 equiv) in toluene (0.26 mL, 1.0 M) yielded **357** as an orange oil (73 mg, 0.22 mmol, 82%). R_f = 0.30 (30% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ –27.5 (*c* 0.26, dichloromethane); IR (film) 2978, 2924, 1697, 1512, 1366, 1134 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.30-7.23 (5H, m, Ar-*H*), 7.08 (2H, d, *J* 8.4, Ar-H), 6.91 (2H, d, *J* 8.5, Ar-H) 5.09 (1H, t, *J* 7.8, CHPh), 3.95-3.80 (1H, m, NC*H*H), 3.62-3.54 (1H, m, NCH*H*), 2.54-2.42 (1H, m, CHPhC*H*H), 2.29 (3H, s, Ar-CH_3), 2.09-1.99 (1H, m, CHPhCH*H*), 1.35 (9H, s, $C(CH_3)_3$); δ*C* (100 MHz; $CDCl_3$) 148.3 (Ar-C) 142.2 (Ar-C), 130.3 (Ar-C), 129.4 (Ar-CH), 128.3 (Ar-CH), 127.1 (Ar-CH), 126.9 (Ar-CH), 115.8 (Ar-CH), 81.0 (C), 63.6 (CH), 53.0 (CH_2), 35.7 (CH_2), 28.2 (CH_3), 20.5 (CH_3), C=O not seen; HRMS (ESI^+) calculated for $C_{21}H_{26}N_2O_2$ $[M+Na]^+$ 361.1892; found 361.1896.

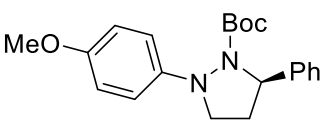


***tert*-Butyl (*R*)-2-([1,1'-biphenyl]-4-yl)-5-phenylpyrazolidine-1-carboxylate (361).** Following general procedure 8, **308** (101 mg, 0.25 mmol, 1.0 equiv), magnesium turnings (30 mg, 1.25 mmol, 5.0 equiv) and methanol (2.5 mL, 0.1 M), then XPhos Pd(crotyl)Cl (8 mg, 12 µmol, 0.05 equiv), sodium *tert*-butoxide (48 mg, 0.50 mmol, 2.0 equiv) and 4-bromobiphenyl (116 mg, 0.50 mmol, 2.0 equiv) in toluene (0.25 mL, 1.0 M) yielded **361** as a colourless oil (73 mg, 0.18 mmol, 73%). R_f = 0.17 (15% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ – 28.2 (*c* 0.19, $CHCl_3$); IR (film) 3030, 2977, 1700, 1608, 1366, 1132 cm^{-1}; δH

(500 MHz; $CDCl_3$) 7.61 (2H, d, *J* 7.4, Ar-H), 7.56 (2H, d, *J* 8.7, Ar-CH), 7.44 (2H, t, *J* 7.7, Ar-CH), 7.31-7.27 (6H, m, Ar-H), 7.10 (2H, d, *J* 8.6, Ar-H), 5.18 (1H, t, *J* 7.6, C*H*Ph), 3.96 (1H, ddd, *J* 10.7, 6.2, 4.2, NC*H*H), 3.74-3.64 (1H, m, NCH*H*), 2.61-2.53 (1H, m, CHPhC*H*H), 2.20-2.10 (1H, m, CHPhCH*H*), 1.41 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 155.9 (C=O), 149.7 (Ar-C), 141.9 (Ar-C), 140.9 (Ar-C), 133.8 (Ar-C), 128.7 (Ar-CH), 128.4 (Ar-CH), 127.5 (Ar-CH), 127.3 (Ar-CH), 126.9 (Ar-CH), 126.6 (Ar-CH), 126.6 (Ar-CH), 115.9 (Ar-CH), 81.4 (C), 63.6 (CH), 52.8 (CH_2), 35.7 (CH_2), 28.2 (CH_3); HRMS (ESI^+) calculated for $C_{26}H_{28}N_2O_2$ $[M+Na]^+$ 423.2043; found 423.2037.

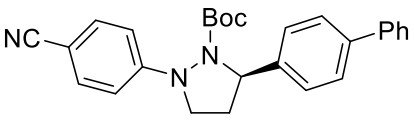


***tert*-Butyl (*R*)-2-(2-cyanophenyl)-5-phenylpyrazolidine-1-carboxylate (359).** Following general procedure 8, **308** (65 mg, 0.26 mmol, 1.0 equiv.), XPhos Pd(crotyl)Cl (18 mg, 26 µmol, 0.1 equiv.), sodium *tert*-butoxide (50 mg, 0.52 mmol, 2.0 equiv.) and 2-bromobenzonitrile (95 mg, 0.52 mmol, 2.0 equiv.) in toluene (0.26 mL, 1.0 M) yielded **359** as a yellow oil (87 mg, 0.25 mmol, 95%). R_f = 0.35 (30% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ + 7.3 (*c* 0.22, Dichloromethane). IR (film) 2971, 2924, 1713, 1450, 1304, 1142 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.56 (1H, dd, *J* 7.7, 1.4, Ar-H), 7.45-7.27 (6H, m, Ar-H), 7.16 (1H, d, *J* 8.3, Ar-H), 6.96 (1H, td, *J* 7.6, 0.9, Ar-H), 5.21 (1H, t, *J* 7.3 C*H*Ph), 4.08-3.90 (2H, m, NCH_2), 2.57 (1H, td, *J* 12.8, 6.4, CHPhC*H*H), 2.21 (1H, td, *J* 14.6, 7.1, CHPhCH*H*), 1.32 (9H, s, $C(CH_3)_3$); δ*C* (100 MHz; $CDCl_3$) 154.4 (Ar-C), 141.3 (Ar-C), 134.3 (Ar-CH), 133.1 (Ar-CH), 128.6 (Ar-CH), 127.5 (Ar-CH), 126.8 (Ar-CH), 121.4 (Ar-CH), 118.6 (Ar-C) 117.3 (Ar-CH), 100.5 (CN), 81.6 (C), 62.5 (CH), 54.4 (CH_2), 34.7 (CH_2), 28.1 (CH_3), C=O not seen; HRMS (ESI^+) calculated for $C_{21}H_{23}N_3O_2$ $[M+Na]^+$ 372.1688; found 372.1690.



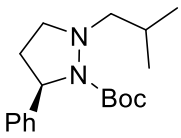
***tert*-Butyl (*R*)-2-(4-methoxyphenyl)-5-phenylpyrazolidine-1-carboxylate (358).** Following general procedure 8, **308** (64 mg, 0.26

mmol, 1.0 equiv.), XPhos Pd(crotyl)Cl (17 mg, 26 µmol, 0.1 equiv.), sodium *tert*-butoxide (50 mg, 0.52 mmol, 2.0 equiv.) and 4-bromoanisole (97 mg, 0.52 mmol, 2.0 equiv.) in toluene (0.26 mL, 1.0 M) yielded **358** as an orange oil (72 mg, 0.20 mmol, 79%). R_f = 0.22 (30% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ – 18.2 (*c* 0.09, Dichloromethane). IR (film) 2924, 2338, 1697, 1504, 1366, 1250 cm^{-1}; δH (400 MHz; $CDCl_3$) 7.28-7.20 (5H, m, Ar-H), 6.96 (2H, dt, *J* 9.4, 3.0, Ar-H), 6.85 (2H, dt, *J* 9.0, 2.2, Ar-H), 5.09 (1H, t, *J* 7.7, C*H*Ph), 3.87-3.80 (1H, m, NC*H*H), 3.79 (3H, s, OCH_3), 3.55 (1H, ddd, *J* 11.4, 9.2, 5.8, NCH*H*), 2.53-2.44 (1H, m, CHPhC*H*H), 2.09-1.99 (1H, m, CHPhCH*H*), 1.35 (9H, s, $C(CH_3)_3$); δ*C* (100 MHz; $CDCl_3$) 154.5 (Ar-C), 144.5 (Ar-C), 142.2 (Ar-C), 128.3 (Ar-CH), 127.1 (Ar-CH), 126.9 (Ar-CH), 117.2 (Ar-CH), 114.2 (Ar-CH), 81.0 (C), 63.6 (CH), 55.6 (CH_3), 53.4 (CH_2), 35.5 (CH_2), 28.2 (CH_3), C=O not seen; HRMS (ESI^+) calculated for $C_{21}H_{26}N_2O_3$ $[M+Na]^+$ 377.1841; found 377.1841.



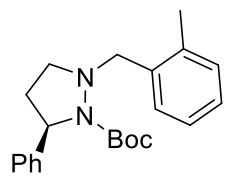
***tert*-Butyl (*R*)-5-([1,1'-biphenyl]-4-yl)-2-(4-cyanophenyl)pyrazolidine-1-carboxylate (365).** To a solution of **312** (40 mg, 0.12 mmol, 1.0 equiv) in methanol (1.2 mL, 0.1 M) was added activated magnesium turnings (15 mg, 0.60 mmol, 5.0 equiv), and the mixture was stirred vigorously (800 rpm) for 2 h at rt. The reaction mixture was quenched with saturated ammonium chloride solution (10 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in toluene (0.12 mL, 1.0 M), and palladium acetate (3 mg, 12 µmol, 0.1 equiv), Xantphos (14 mg, 25 µmol, 0.2 equiv), sodium *tert*-butoxide (24 mg, 0.25 mmol, 2.0 equiv) and 4-bromobenzonitrile (45 mg, 0.25 mmol, 2.0 equiv) were added. The solution was stirred at 90 °C for 20 h. The reaction mixture was then quenched with saturated ammonium chloride solution (5 mL), extracted with dichloromethane (3 × 5 mL), dried over magnesium sulphate and then concentrated *in vacuo*. The crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to give **365** as a

colourless oil (45 mg, 0.11 mmol, 86%). R_f = 0.23 (25% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ –10.7 (*c* 0.42, $CHCl_3$); IR (film) 2977, 2928, 2218, 1705, 1603, 1509, 1338, 1142 cm^{-1}; δH (500 MHz; $CDCl_3$) 7.48 (4H, dd, *J* 8.0, 4.8, Ar-H), 7.44 (2H, d, *J* 8.2, Ar-H), 7.35 (2H, t, *J* 7.6, Ar-H), 7.27 (1H, t, *J* 7.4, Ar-H), 7.21 (2H, d, *J* 8.2, Ar-H), 6.86 (2H, d, *J* 8.8, Ar-H), 5.26 (1H, t, *J* 6.9, CHPh), 3.77-3.70 (1H, m, NC*H*H), 3.66 (1H, dt, *J* 10.5, 7.4, NCH*H*), 2.53 (1H, td, *J* 12.5, 7.1, CHPhC*H*H), 2.23-2.12 (1H, m, CHPhCH*H*), 1.36 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 152.8 (C=O), 140.5 (Ar-C), 139.8 (Ar-C), 133.2 (Ar-C), 128.8 (Ar-CH), 127.4 (Ar-CH), 127.3 (Ar-CH), 127.0 (Ar-CH), 127.0 (Ar-CH), 126.6 (Ar-C), 126.6 (Ar-CH), 119.9 (Ar-C) 114.2 (Ar-CH), 102.1 (CN), 82.3 (C), 62.8 (CH), 50.6 (CH_2), 35.1 (CH_2), 28.2 (CH_3); HRMS (ESI^+) calculated for $C_{27}H_{27}N_3O_2$ $[M+Na]^+$ 448.1995; found 448.1999.



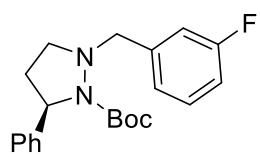
***tert*-Butyl (*R*)-2-isobutyl-5-phenylpyrazolidine-1-carboxylate (369).** Cyclic hydrazine **308** (84 mg, 0.20 mmol, 1.0 equiv), activated magnesium turnings (24 mg, 1.0 mmol, 5.0 equiv) and methanol (2.0 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. To this was added sodium triacetoxyborohydride (212 mg, 1.00 mmol, 5.0 equiv), isobutyraldehyde (91 µL, 1.0 mmol, 5.0 equiv) and tetrahydrofuran (2 mL, 0.1 M). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with 1 M NaOH (5 mL), extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography twice (5-10% ethyl acetate in petroleum ether) to give **369** as a colourless oil (39 mg, 0.13 mmol, 63%). R_f = 0.38 (15% ethyl acetate in heptane). $[\alpha]^{32}_D$ +35.8 (*c* 0.30, dichloromethane). IR (film) 2955, 2878, 1690, 1366, 1173 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.39-7.15 (5H, m, Ar-*H*), 4.97 (1H, t, *J* 8.4, C*H*Ph), 3.15 (1H, td, *J* 11.3, 5.9, NC*H*HCH_2), 3.03

(1H, ddd, *J* 11.6, 6.6, 2.3, NCH*H*CH_2), 2.71 (1H, dd, *J* 11.5, 7.1, NC*H*HCH$(CH_3)_2$), 2.56-2.43 (2H, m, NCH*H*CH$(CH_3)_2$ and C*H*HCHPh), 2.23-2.10 (1H, m, CH*H*CHPh), 1.80 (1H, nonet, *J* 7.0, C*H*$(CH_3)_2$), 1.36 (9H, s, C$(CH_3)_3$), 1.05 (3H, d, *J* 6.6, CHC*H*$_3$), 1.02 (3H, d, *J* 6.6, CHC*H*$_3$); δ*C* (100 MHz; $CDCl_3$) 143.8 (Ar-C), 128.3 (Ar-CH), 126.6 (Ar-CH), 125.7 (Ar-CH), 80.1 (C), 66.8 (CH_2), 63.1 (CH), 53.3 (CH_2), 34.9 (CH_2), 28.3 (CH_3), 27.5 (CH), 21.3 (CH_3), 20.9 (CH_3), C=O not seen; HRMS (ESI^+) calculated for $C_{18}H_{28}N_2O_2$ $[M+Na]^+$ 327.2048; found 327.2052.



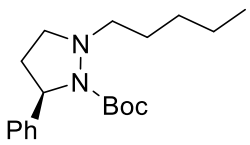
***tert*-Butyl (*R*)-2-(2-methylbenzyl)-5-phenylpyrazolidine-1-carboxylate (367).** Cyclic hydrazine **308** (40 mg, 0.16 mmol, 1.0 equiv), activated magnesium turnings (19 mg, 0.8 mmol, 5.0 equiv) and methanol (1.6 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. To this was added sodium triacetoxyborohydride (170 mg, 0.80 mmol, 5.0 equiv.), 2-tolualdehyde (93 µL, 0.80 mmol, 5.0 equiv.) in tetrahydrofuran (0.16 mL, 1.0 M). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with 1 M NaOH (5 mL), extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography twice (20% ethyl acetate in hexane) to give **367** as a colourless oil (18 mg, 50 µmol, 32%). R_f = 0.35 (20% ethyl actate in hexane). $[\alpha]^{32}_D$ + 28.7 (*c* 0.06, CH_2Cl_2). IR (film) 2970, 2924, 1697, 1366, 1134 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.41-7.22 (6H, m, Ar-*H*), 7.19-7.06 (3H, m, Ar-*H*), 5.02 (1H, t, *J* 8.2 C*H*Ph), 4.15 (1H, d, *J* 11.9, NC*H*HAr), 3.88 (1H, d, *J* 11.9, NCH*H*Ar), 3.06 (1H, ddd, J 11.8, 6.2, 2.8, NC*H*H), 3.00-2.89 (1H, m, NCH*H*), 2.60-2.49 (1H, m, CHPhC*H*H and CH_3), 2.30-2.17 (1H, m, CHPhCH*H*), 1.33 (9H, s, C$(CH_3)_3$); δ*C* (100 MHz; $CDCl_3$) 143.7 (Ar-C), 138.2 (Ar-C), 135.6 (Ar-C), 130.9 (Ar-CH),

130.4 (Ar-CH), 128.4 (Ar-CH), 127.7 (Ar-CH), 126.8 (Ar-CH), 125.8 (Ar-CH), 125.6 (Ar-CH), 80.3 (C), 63.5 (CH), 59.3 (CH_2), 50.4 (CH_2), 34.6 (CH_2), 28.3 (CH_3), 19.5 (CH_3), C=O not seen; HRMS (ESI^+) calculated for $C_{22}H_{28}N_2O_2$ $[M+Na]^+$ 375.2048; found 375.2049.

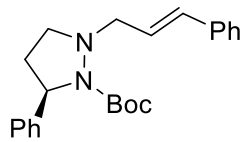


***tert*-Butyl (*R*)-2-(3-fluorobenzyl)-5-phenylpyrazolidine-1-carboxylate (368).** Cyclic hydrazine **308** (40 mg, 0.16 mmol, 1.0 equiv.), activated magnesium turnings (19 mg, 0.8 mmol, 5.0 equiv) and methanol (1.6 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. To this was added sodium triacetoxyborohydride (170 mg, 0.80 mmol, 5.0 equiv.), 3-fluorobenzaldehyde (72 µL, 0.80 mmol, 5.0 equiv.) and tetrahydrofuran (1.6 mL, 0.1 M). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with 1 M NaOH (5 mL), extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography twice (15% ethyl acetate in heptane) to give **368** as a colourless oil (24 mg, 70 µmol, 42%). R_f = 0.35 (15% ethyl acetate in heptane). $[\alpha]^{32}_D$ + 40.0 (*c* 0.27, Dichloromethane). IR (film) 2970, 2924, 1697, 1366, 1142 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.39-7.17 (8H, m, Ar-*H*), 6.97 (1H, dd, *J* 8.2 and 2.1, Ar-*H*), 5.00 (1H, t, *J* 8.0 C*H*Ph), 4.16 (1H, d, *J* 12.4, NC*H*HAr), 3.85 (1H, d, *J* 12.4, NCH*H*Ar), 3.09-2.98 (2H, m, NCH_2), 2.55-2.49 (1H, m, CHPhC*H*H), 2.28-2.14 (1H, m, CHPhCH*H*), 1.34 (9H, s, $C(CH_3)_3$); δ*C* (100 MHz; $CDCl_3$) 162.9 (d, *J* 244, Ar-CF), 154.9 (C=O), 143.4 (Ar-C), 140.4 (d, *J* 8.0, Ar-C), 129.7 (d, *J* 8.0, Ar-CH), 128.4 (Ar-CH), 126.9 (Ar-CH), 125.8 (Ar-CH), 125.0 (d, *J* 2.0, Ar-CH), 116.4 (d, *J* 22.0, Ar-CH), 114.4 (d, *J* 21, Ar-CH), 80.4 (C), 63.3 (CH), 61.2 (CH_2), 51.2 (CH_2), 34.7 (CH_2), 28.3 (CH_3); δ*F* (376

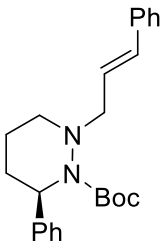
MHz; $CDCl_3$) -113.5 (CF); HRMS (ESI^+) calculated for $C_{21}H_{25}N_2NaFO_2$ $[M+Na]^+$ 379.1798; found 379.1800.



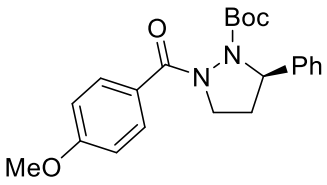
***tert*-Butyl (*R*)-2-pentyl-5-phenylpyrazolidine-1-carboxylate (371).** Cyclic hydrazine **308** (75 mg, 0.30 mmol, 1.0 equiv.), activated magnesium turnings (36 mg, 1.5 mmol, 5.0 equiv) and methanol (3.0 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. To this was added sodium triacetoxyborohydride (370 mg, 1.51 mmol, 5.0 equiv.), valeraldehyde (161 µL, 1.51 mmol, 5.0 equiv.) and tetrahydrofuran (3.0 mL, 0.1 M). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with 1 M NaOH (5 mL), extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography twice (15% ethyl acetate in heptane) to give **XX** as a colourless oil (54 mg, 0.17 mmol, 56%). R_f = 0.38 (15% ethyl acetate in heptane). $[\alpha]^{32}_D$ + 35.5 (*c* 0.17, Dichloromethane). IR (film) 2932, 2862, 1697, 1366, 1173 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.35-7.19 (5H, m, Ar-*H*), 4.96 (1H, t, *J* 8.2, C*H*Ph), 3.20-3.13 (1H, m, NC*H*H), 3.10-3.04 (1H, m, NCH*H*), 2.91 (1H, dt, *J* 11.3, 7.7, NC*H*H$(CH_2)_3$), 2.71 (1H, dt, *J* 11.3, 7.7, NCH*H*$(CH_2)_3$), 2.55-2.45 (1H, m, CHArC*H*H), 2.20-2.10 (1H, m, CHArCH*H*), 1.61 (2H, quin, *J* 7.1, CH_2), 1.41-1.28 (4H, m, 2 x CH_2), 0.92 (3H, t, *J* 7.3, CH_2CH_3); δ*C* (100 MHz; $CDCl_3$) 154.4 (C=O seen by HMBC), 142.7 (Ar-C), 127.3 (Ar-CH), 125.7 (Ar-CH), 124.7 (Ar-CH), 79.1 (C), 62.2 (CH), 57.4 (CH_2), 52.9 (CH_2) 33.9 (CH_2), 28.5 (CH_2), 27.2 (CH_3), 21.7 (CH_2), 13.0 (CH_3), 1 CH_2 not seen; HRMS (ESI^+) calculated for $C_{19}H_{30}N_2NaO_2$ $[M+Na]^+$ 341.2205; found 341.2210.



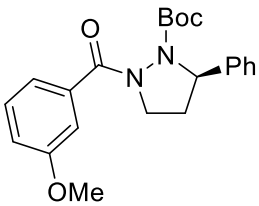
***tert*-Butyl (*R*)-2-cinnamyl-5-phenylpyrazolidine-1-carboxylate (370).** Cyclic hydrazine **308** (75 mg, 0.30 mmol, 1.0 equiv.), activated magnesium turnings (36 mg, 1.5 mmol, 5.0 equiv) and methanol (3.0 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. To this was added sodium triacetoxyborohydride (320 mg, 1.51 mmol, 5.0 equiv.), cinnamaldehyde (191 µL, 1.51 mmol, 5.0 equiv.) and tetrahydrofuran (3 mL, 0.1 M). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with 1 M NaOH (5 mL), extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (15% ethyl acetate in hexane) to give **370** as a colourless oil (84 mg, 0.26 mmol, 76%). R_f = 0.36 (15% ethyl acetate in hexane). $[\alpha]^{32}_D$ + 42.9 (*c* 0.02, Dichloromethane). IR (film) 2963, 2924, 1697, 1366, 1134 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.41-7.20 (10H, m, Ar-*H*), 6.53 (1H, d, *J* 16.1, C*H*CHCH$_2$), 6.44 (1H, dt, *J* 15.9, 6.3, CHC*H*CH$_2$), 4.98 (1H, t, *J* 7.9, C*H*Ph), 3.77 (1H, dd, *J* 12.7, 5.8, NC*H*HCH), 3.57 (1H, dd, *J* 12.8, 6.8, NCH*H*CH), 3.25-3.14 (2H, m, NCH$_2$C*H*$_2$), 2.55 (1H, qd, *J* 9.0, 4.7, NC*H*HCH$_2$), 2.17 (1H, dq, J 12.5, 8.3, NCH*H*CH$_2$), 1.30 (9H, s, C(CH$_3$)$_3$); δ*C* (100 MHz; $CDCl_3$) 143.5 (Ar-C), 136.9 (Ar-C), 133.1 (CH), 128.6 (Ar-CH), 128.4 (Ar-CH), 127.6 (Ar-CH), 126.8 (CH), 126.5 (Ar-CH), 126.4 (Ar-CH), 125.8 (Ar-CH), 80.3 (C), 63.2 (CH) 60.5 (CH$_2$), 51.5 (CH$_2$), 34.9 (*C*H$_2$), 28.2 (*C*H$_3$), C=O not seen; HRMS (ESI^+) calculated for $C_{23}H_{28}N_2NaO_2$ $[M+Na]^+$ 387.2048; found 387.2050.



***tert*-Butyl (*R*)-2-cinnamyl-6-phenyltetrahydropyridazine-1(*2H*)-carboxylate (440).** Cyclic hydrazine **332** (134 mg, 0.31 mmol, 1.0 equiv), activated magnesium turnings (38 mg, 1.55 mmol, 5.0 equiv) and methanol (3.1 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 h. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a colourless oil. To this was added sodium triacetoxyborohydride (323 mg, 1.52 mmol, 5.0 equiv), *E*-cinnamaldehyde (193 µL, 1.52 mmol, 5.0 equiv) and tetrahydrofuran (3.1 mL, 0.1 M). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with 1 M NaOH (5 mL), extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (5-10% ethyl acetate in petroleum ether) to give **440** as a colourless oil (105 mg, 0.28 mmol, 91%). R_f = 0.16 (10% ethyl acetate in heptane); $[\alpha]^{32}_D$ +24.0 (*c* 0.35, $CHCl_3$). IR (film) 3007, 2866, 1681, 1390, 1069 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.48-7.43 (2H, m, Ar-*H*), 7.35 (2H, t, *J* 7.5, Ar-H), 7.32-7.27 (5H, m, Ar-H), 7.25-7.20 (1H, m, Ar-H), 6.22 (1H, d, *J* 15.9, C=CH), 6.09 (1H, dt, *J* 15.8, 6.3, C=CH), 5.37 (1H, s, C*H*Ph), 3.58 (2H, d, *J* 7.0, NC*H*$_2$CH=C), 3.22-3.07 (1H, m, NC*H*HCH$_2$), 2.99-2.92 (1H, m, NCH*H*CH$_2$), 2.42-2.21 (1H, m, C*H*HCHPh), 2.09-1.95 (2H, m, CH*H*CHPh and NCH$_2$C*H*H), 1.53 (10H, s, NCH$_2$CH*H* and C(CH$_3$)$_3$); δ*C* (125 MHz; $CDCl_3$) 142.0 (Ar-C), 137.2 (Ar-C), 131.7 (C=CH) 128.5 (Ar-CH), 128.2 (Ar-CH), 127.4 (C=CH), 127.2 (Ar-CH), 127.1 (Ar-CH), 126.6 (Ar-CH), 126.3 (Ar-CH), 80.5 (C), 57.9 (CH_2), 55.2 (CH, seen on HSQC), 49.0 (CH_2), 29.7 (CH_2), 28.5 (CH_3), 25.6 (CH_2), 17.9 (CH_3), C=O not seen; HRMS (ESI^+) calculated for $C_{24}H_{30}N_2O_2$ $[M+Na]^+$ 401.2199; found 401.2197.

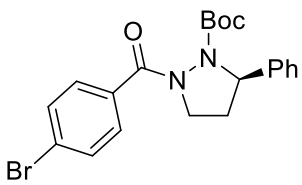


***tert*-Butyl (*R*)-2-(4-methoxybenzoyl)-5-phenylpyrazolidine-1-carboxylate (373).** Cyclic hydrazine **308** (36 mg, 90 µmol, 1.0 equiv), magnesium turnings (11 mg, 0.45 mmol, 5.0 equiv) and methanol (0.9 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over magnesium sulphate and concentrated *in vacuo* to give a colourless oil. Then a solution of 4-methoxybenzoyl chloride (30 µL, 0.23 mmol, 2.5 equiv) in dichloromethane (0.9 mL) were added. The reaction mixture was stirred at rt for 18 h. The mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to give **373** as a colourless oil (27 mg, 70 µmol, 80%). R_f = 0.21 (25% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ +19.6 (*c* 0.18, dichloromethane); IR (film) 2989, 2924, 1712, 1611, 1388, 1161 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.58-7.49 (2H, m, Ar-H), 7.36-7.23 (5H, m, Ar-*H*), 6.79 (2H, d, *J* 8.4, Ar-H), 5.32 (1H, br s, C*H*Ph), 4.34-4.17 (1H, m, NC*H*H), 3.81 (3H, s, OCH_3), 3.54 (1H, d, *J* 8.6, NCH*H*), 2.55 (1H, dtd, *J* 12.5, 8.3, 4.2, CHPhC*H*H), 2.27 (1H, br s, CHPhCH*H*), 1.35 (9H, s, $C(CH_3)_3$); δ*C* (100 MHz; $CDCl_3$) 161.6 (C=O), 140.6 (Ar-C), 132.2 (Ar-C), 130.2 (Ar-CH), 128.6 (Ar-CH), 127.5 (Ar-CH), 126.5 (Ar-CH), 113.1 (Ar-CH), 82.3 (C), 62.9 (CH), 55.3 (CH_3), 36.2 (CH_2), 28.0 (CH_3), C=O, Ar-C and CH_2 not seen; HRMS (ESI^+) calculated for $C_{22}H_{26}N_2O_4$ $[M+Na]^+$ 405.1790; found 405.1793.



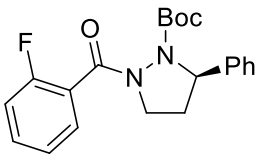
***tert*-butyl (*R*)-2-(3-methoxybenzoyl)-5-phenylpyrazolidine-1-carboxylate (374).** Cyclic hydrazine **308** (22 mg, 90 µmol, 1.0 equiv.), magnesium turnings (11 mg, 0.45 mmol, 5.0 equiv) and methanol (0.9 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The

combined organic extracts were dried over magnesium sulphate and concentrated *in vacuo* to give a colourless oil. 4-methoxybenzoyl chloride (30 µL, 0.23 mmol, 2.5 equiv.) and dichloromethane (5 mL) were added. The reaction mixture was stirred at rt for 18 h. The mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to give **374** as a colourless oil (21 mg, 64 µmol, 71%). R_f = 0.23 (25% ethyl acetate in petroleum ether). $[\alpha]^{32}_D$ + 5.7 (*c* 0.40, CH_2Cl_2). IR (film) 2989, 2922, 1712, 1617, 1378, 1161 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.40-7.27 (5H, m, Ar-H), 7.24-6.87 (4H, m, Ar-*H*), 5.35 (1H, br s, C*H*Ph), 4.63-4.05 (1H, m, NC*H*H), 3.71-3.45 (4H, m, OCH_3 and NCH*H*), 2.73-2.48 (1H, m, CHPhC*H*H), 2.32 (1H, br s, CHPhCH*H*), 1.35 (9H, s, $C(CH_3)_3$); δ*C* (100 MHz; $CDCl_3$) 159.0 (C=O), 136.0 (Ar-C), 128.9 (Ar-CH), 128.7 (Ar-CH), 127.6 (Ar-CH), 126.7 (Ar-CH), 120.5 (Ar-CH), 117.2 (Ar-CH), 82.5 (C), 62.8 (CH), 55.2 (CH_3), 28.0 (CH_3), 2 x CH_2, 2 x Ar-C and 1 C=O not seen; HRMS (ESI^+) calculated for $C_{22}H_{26}N_2O_4$ $[M+Na]^+$ 405.1790; found 405.1790.



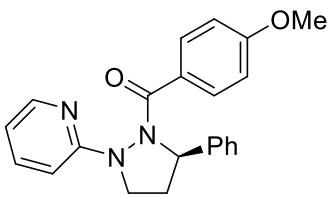
***tert*-Butyl (*R*)-2-(4-bromobenzoyl)-5-phenylpyrazolidine-1-carboxylate (375).** Cyclic hydrazine **308** (68 mg, 0.27 mmol, 1.0 equiv.), magnesium turnings (33 mg, 1.35 mmol, 5.0 equiv) and methanol (2.7 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over magnesium sulphate and concentrated *in vacuo* to give a colourless oil. 4-bromoxybenzoyl chloride (150 mg, 0.69 mmol, 2.5 equiv.) and dichloromethane (2.7 mL, 0.1 M) were added. The reaction mixture was stirred at rt for 18 h. The mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to give **375** as a colourless oil (21 mg, 55 µmol, 61%). R_f = 0.24 (25% ethyl acetate in petroleum ether). $[\alpha]^{32}_D$ + 32.3 (*c* 0.12, CH_2Cl_2). IR (film) 2978, 2932, 1721, 1659, 1366, 1157 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.42-

7.15 (9H, m, Ar-H), 5.37 (1H, br s, C*H*Ph), 4.49-4.08 (1H, m, NC*H*H), 3.53 (1H, q, *J* 8.3, NCH*H*), 2.63-2.48 (1H, m, CHPhC*H*H), 2.38 (1H, br s, CHPhCH*H*), 1.36 (9H, s, $C(CH_3)_3$); δ*C* (100 MHz; $CDCl_3$) 133.7 (Ar-C), 131.8 (Ar-C), 130.9 (Ar-CH), 129.6 (Ar-CH), 128.7 (Ar-CH), 127.8 (Ar-CH), 126.7 (Ar-CH), 82.8 (C), 62.9 (CH), 28.0 (CH_3), 2 x CH_2, 2 x C=O and 1 x Ar-C not seen; HRMS (ESI^+) calculated for $C_{21}H_{23}N_2O_2Br^{79}$ $[M+Na]^+$ 453.0790; found 453.0791.



***tert*-Butyl (*R*)-2-(2-fluorobenzoyl)-5-phenylpyrazolidine-1-carboxylate (376).** Cyclic hydrazine **308** (64 mg, 0.16 mmol, 1.0 equiv), magnesium turnings (19 mg, 0.80 mmol, 5.0 equiv) and methanol (1.6 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extrcts were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. To this was added then 2-fluorobenzoyl chloride (48 µL, 0.40 mmol, 2.5 equiv) in dichloromethane (1.6 mL). The reaction mixture was stirred at rt for 18 h. The mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to give **376** as a colourless oil (46 mg, 0.12 mmol, 77%). R_f = 0.21 (25% ethyl acetate in petroleum ether). $[\alpha]^{32}_D$ +7.1 (*c* 0.12, $CHCl_3$). IR (film) 2978, 1725, 1714, 1368, 1154 cm^{-1}; δ*H* (500 MHz; d6-DMSO at 373 K) 7.47 (1H, d, *J* 5.3, Ar-H), 7.39-7.25 (5H, m, Ar-H), 7.25-7.13 (3H, m, Ar-H), 5.27 (1H, t, *J* 6.6, C*H*Ph), 4.05-3.91 (1H, br m, NC*H*H), 3.47 (1H, dd, *J* 17.9 and 8.5, NCH*H*), 2.69-2.60 (1H, m, CHPhC*H*H), 2.23-2.16 (1H, br m, CHPhCH*H*), 1.38 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; d6-DMSO at 373 K) 159.9 (C=O), 157.9 (C=O), 143.7 (Ar-C, seen on HMBC), 141.7 (Ar-C, seen on HMBC), 141.3 (Ar-C, seen on HMBC), 132.5 (d, *J* 7.5, Ar-CH), 129.2 (d, *J* 2.5, Ar-CH), 129.1 (Ar-CH), 128.7 (Ar-CH), 127.6 (Ar-CH), 127.0 (Ar-CH), 126.7 (Ar-CH), 116.2 (d, *J* 21.3, 82.1 Ar-C), 63.5 (CH), 28.0 (CH_3), 2 x CH_2, 2 x C=O and 1 x Ar-C not seen; δ*F* (282 MHz;

$CDCl_3$) -112.3 (CF); HRMS (ESI^+) calculated for $C_{21}H_{23}N_2O_3F$ $[M+Na]^+$ 393.1585; found 393.1587.

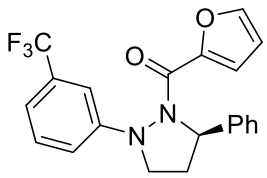


(*R*)-(4-Methoxyphenyl)(5-phenyl-2-(pyridin-2-yl)pyrazolidin-1-yl)methanone (377). Cyclic hydrazine **354** (29 mg, 90 µmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2 mL) and stirred for 2 h. It was then concentrated *in vacuo* and 4-methoxybenzoyl chloride (38 mg, 0.23 mmol, 2.5 equiv) in dichloromethane (90 µL, 0.1 M) was added. The reaction mixture was cooled over an ice bath then *N*,*N*-diisopropylethylamine (31 µL, 0.18 mmol, 2.0 equiv) in dichloromethane (2 mL) was added dropwise over 30 min. The reaction mixture was allowed to warm to rt then stirred for 18 h. The mixture was then quenched with 1 M hydrochloric acid (5 mL), extracted with dichloromethane (3 x 5 mL) and dried over $MgSO_4$. It was then concentrated *in vacuo* and the crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to give **377** as a white solid (26 mg, 70 µmol, 82%). R_f = 0.21 (25% ethyl acetate in petroleum ether); M.p. 131-132 °C; $[\alpha]^{32}_D$ –26.7 (*c* 0.06, CH_2Cl_2). IR (film) 2924, 1643, 1597, 1466, 1258 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 8.25 (1H, d, *J* 4.0, Ar-H), 7.78 (2H, d, *J* 8.4, Ar-H), 7.45 (1H, t, *J* 7.6, Ar-H), 7.26-7.19 (5H, m, Ar-*H*), 6.88-6.74 (4H, m, Ar-H), 5.60 (1H, s, C*H*Ph), 4.65 (1H, br s, NC*H*H), 3.78 (3H, s, OCH_3), 3.60 (1H, s, NCH*H*), 2.63 (1H, dt, *J* 12.4, 6.1, CHPhC*H*H), 2.22 (1H, td, *J* 13.4, 7.2, CHPhCH*H*); δ*C* (100 MHz; $CDCl_3$) 161.9 (C=O), 147.8 (Ar-CH), 141.0 (Ar-C), 137.5 (Ar-CH), 130.7 (Ar-C), 128.5 (Ar-CH), 127.3 (Ar-CH), 126.9 (Ar-CH), 126.4 (Ar-C), 116.4 (Ar-CH), 113.3 (Ar-CH), 110.6 (Ar-CH), 69.6 (CH), 55.3 (CH_3), 34.0 (CH_2), 1 Ar-CH, 1 CH_2 and 1 Ar-C not seen; HRMS (ESI^+) calculated for $C_{22}H_{21}N_3O_2$ $[M+H]^+$ 360.1712; found 360.1712.

Crystal Structure of **377.** Single crystals of $C_{44}H_{42.5}N_6O_{4.25}$ were grown from a 9:1 mix of hexane and isopropanol. A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a duel source (Cu at zero) equipped with an

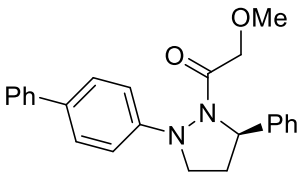
AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Crystal Data for $C_{44}H_{42.5}N_6O_{4.25}$ (M =723.34 g/mol): monoclinic, space group $P2_1$ (no. 4), *a* = 10.18405(5) Å, *b* = 9.71457(5) Å, *c* = 18.82762(9) Å, β = 93.0169(4)°, V = 1860.102(16) Å3, Z = 2, T = 150(2) K, μ(CuKα) = 0.679 mm^{-1}, *Dcalc* = 1.291 g/cm^3, 35330 reflections measured (8.694° ≤ 2Θ ≤ 147.052°), 7385 unique (R_{int} = 0.0176, R_{sigma} = 0.0104) which were used in all calculations. The final R_1 was 0.0257 (I > 2σ(I)) and *w*R_2 was 0.0682 (all data). Data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1944269.

Flack x: -0.05(3) Shelx2018, Hooft y: -0.045(2) Olex2. Both the Flack parameter and associated Hooft y parameter are realtively small for a structure with no heavy atoms, so confidence in the handedness of the chiral centre is high.



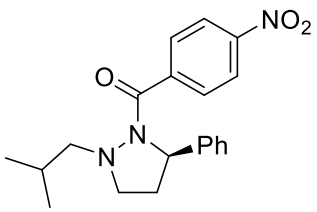
(*R*)-Furan-2-yl(5-phenyl-2-(3-(trifluoromethyl)phenyl)pyrazolidin-1-yl)methanone (378). Cyclic hydrazine **360** (41 mg, 0.10 mmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2 mL) and stirred for 2 h. It was then concentrated *in vacuo* then 2-furoyl chloride (26 μL, 0.26 mmol, 2.5 equiv) and dichloromethane (100 μL, 0.1 M) were added. The reaction mixture was cooled over an ice bath then a solution of *N*,*N*-diisopropylethylamine (37 μL, 0.21 mmol, 2.0 equiv) in dichloromethane (2 mL) was added dropwise over 30 minutes. The mixture was allowed to warm to rt then stirred for 18 h. The mixture was then quenched with 1 M hydrochloric acid (5 mL), extracted with dichloromethane (3 × 5 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo* and the crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to give **378** as a yellow solid (28 mg, 71 μmol, 69%). R_f = 0.18 (25% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ +0.9 (*c* 0.33, $CHCl_3$). IR (film) 2927, 1649, 1470, 1337, 1124 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.55 (1H, s, Ar-H), 7.40-7.21 (9H, m, Ar-H), 6.95 (1H, d, *J* 3.0, Ar-*H*), 6.38 (1H, dd, *J* 3.5 and 1.6, Ar-H), 5.75 (1H, t, *J* 8.2, C*H*Ph), 4.12-4.07 (1H, br m, NC*H*H), 3.62-3.48 (1H, br m, NCH*H*), 2.68-2.62

(1H, m, CHPhC*H*H), 2.37-2.28 (1H, m, CHPhCH*H*); δ*C* (125 MHz; $CDCl_3$) 162.5 (C=O, seen on HMBC), 150.3 (Ar-C), 145.7 (Ar-CH), 139.8 (Ar-C), 131.6 (q, *J* 31.3, Ar-C), 129.7 (Ar-CH), 128.4 (Ar-CH), 127.6 (Ar-CH), 123.9 (q, *J* 270, Ar-C), 119.5 (Ar-CH), 118.7 (Ar-CH), 118.2 (Ar-CH), 112.9 (Ar-CH), 111.7 (Ar-CH), 62.5 (CH), 54.3 (CH_2), 32.6 (CH_2), 1 Ar-C and 1 Ar-CH not seen; δ*F* (282 MHz; $CDCl_3$) -62.8 (CF_3); HRMS (ESI^+) calculated for $F_3C_{21}H_{17}N_2O_2$ $[M+Na]^+$ 409.1134; found 409.1131.



(*R*)-1-(2-([1,1'-Biphenyl]-4-yl)-5-phenylpyrazolidin-1-yl)-2-methoxyethan-1-one (379). Cyclic hydrazine **361** (45 mg, 0.11 mmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2.0 mL) and stirred for 2 h. It was then concentrated *in vacuo* and methoxyacetyl chloride (26 µL, 0.28 mmol, 2.5 equiv) and dichloromethane (110 µL, 0.1 M) were added. The reaction mixture was cooled over an ice bath then a solution of *N*,*N*-diisopropylethylamine (39 µL, 0.22 mmol, 2.0 equiv) in dichloromethane (2.0 mL) was added dropwise over 30 minutes. The reaction mixture was allowed to warm to rt then stirred for 18 h. The reaction mixture was then quenched with 1 M hydrochloric acid (5 mL), extracted with dichloromethane (3 × 5 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo* and the crude product was purified by column chromatography (50% ethyl acetate in petroleum ether) to give **379** as a white solid (28 mg, 74 µmol, 66%). R_f = 0.16 (50% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ –17.5 (*c* 0.35, $CHCl_3$). IR (film) 2926, 1686, 1485, 1197, 1128 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.57 (2H, d, *J* 7.3, Ar-H), 7.51 (2H, d, *J* 8.4, Ar-CH), 7.46-7.38 (4H, m, Ar-H), 7.37-7.23 (4H, m, Ar-*H*), 7.06 (2H, d, *J* 8.5, Ar-H), 5.46 (1H, t, *J* 8.5, C*H*Ph), 4.48 (1H, d, J 15.5, NC*H*H), 4.06 (2H, d, *J* 15.6, CH_2OMe) 3.49-3.43 (4H, m, NCH*H* and OCH_3), 2.63-2.56 (1H, m, CHPhC*H*H), 2.35-2.25 (1H, br m, CHPhCH*H*); δ*C* (125 MHz; $CDCl_3$) 174.5 (C=O), 148.9 (Ar-C), 140.3 (Ar-C), 140.1 (Ar-C), 135.0 (Ar-C), 128.8 (Ar-CH), 128.4 (Ar-CH), 127.8 (Ar-CH), 127.5 (Ar-CH), 127.0 (Ar-CH), 126.7 (Ar-CH), 116.3 (Ar-CH), 70.5 (CH_2), 61.8 (CH), 59.4 (OCH_3), 54.4

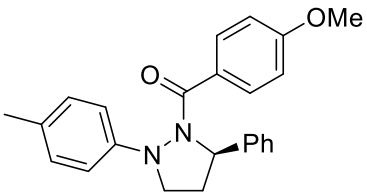
(CH_2), 32.0 (CH_2), 1 Ar-CH not seen; HRMS (ESI^+) calculated for $C_{24}H_{24}N_2O_2$ $[M+Na]^+$ 395.1730; found 395.1721.



(*R*)-(2-Isobutyl-5-phenylpyrazolidin-1-yl)(4-nitrophenyl)methanone (380). Cyclic hydrazine **369** (43 mg, 0.14 mmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2 mL) and stirred for 2 h. It was then concentrated *in vacuo* and a solution of 4-nitrobenzoyl chloride (63 mg, 0.34 mmol, 2.5 equiv) in dichloromethane (135 µL, 0.1 M) were added. The mixture was cooled over an ice bath then *N*,*N*-diisopropylethylamine (47 µL, 0.27 mmol, 2.0 equiv) in dichloromethane (2.0 mL) was added dropwise over 30 minutes. The reaction mixture was allowed to warm to rt then stirred for 18 h. The reaction mixture was then quenched with 1 M hydrochloric acid (5 mL), extracted with dichloromethane (3 × 5 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo* and the crude product was purified by column chromatography (20% ethyl acetate in petroleum ether) to give **380** as a white solid (37 mg, 0.1 mmol, 77%). R_f = 0.18 (20% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ + 5.2 (*c* 0.17, $CHCl_3$); Enantiomeric excess (95% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 10/90; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 17.4 min; t_R 36.3 min; IR (film) 2923, 2851, 1635, 1521, 1346 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 8.24 (2H, d, *J* 8.6, Ar-H), 7.84-7.74 (2H, br m, Ar-H), 7.33 (5H, br m, Ar-H), 5.48 (1H, br s, C*H*Ph), 3.24-3.09 (1H, br m, NC$H_2$$CH_2$), 2.83-2.74 (1H, br m, CHPhC*H*H), 2.49-2.29 (3H, br m, CHPhCH*H* and CH_2CH(CH_3)$_2$) 1.45 (1H, br s, C*H*(CH_3)$_2$), 0.55 (6H, s, CH(CH_3)$_2$); δ*C* (125 MHz; $CDCl_3$) 166.6 (C=O), 148.2 (Ar-C), 142.8 (Ar-C), 142.1 (Ar-C), 129.0 (Ar-CH), 128.6 (Ar-CH), 125.7 (Ar-CH), 123.6 (Ar-CH), 122.9 (Ar-CH), 65.8 (CH_2), 61.8 (CH), 33.2 (CH_2), 27.2 (CH), 20.5 (CH_3), 20.2 (CH_3), 1 CH_2 not seen; HRMS (ESI^+) calculated for $C_{20}H_{23}N_3O_3$ $[M+Na]^+$ 376.1632; found 376.1632.

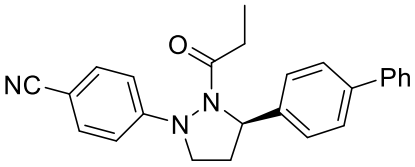
Crystal Structure of (*rac*)**-380.** Single crystals of $C_{20}H_{23}N_3O_3$ were grown from 9:1 hexane and isopropanol. A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a duel source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL refinement package using Least Squares minimisation. Crystal Data for $C_{20}H_{23}N_3O_3$ (M =353.41 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 7.19100(10) Å, b = 13.50450(10) Å, c = 18.6644(2) Å, V = 1812.52(3) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 0.716 mm^{-1}, *Dcalc* = 1.295 g/cm^3, 10496 reflections measured ($8.082° \leq 2\Theta \leq 147.174°$), 3514 unique ($R_{int}$ = 0.0227, R_{sigma} = 0.0229) which were used in all calculations. The final R_1 was 0.0325 ($I > 2\sigma(I)$) and wR_2 was 0.1083 (all data). Data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1944270.

As the crystal was grown from a racemate the Flack parameter was not determined.



(*R*)-(4-Methoxyphenyl)(5-phenyl-2-(*p*-tolyl)pyrazolidin-1-yl)methanone (381). Cyclic hydrazine **357** (34 mg, 0.1 mmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2 mL) and stirred for 2 h. It was then concentrated *in vacuo* and 4-methoxybenzoyl chloride (34 μL, 0.25 mmol, 2.5 equiv) and dichloromethane (100 μL, 0.1 M) were added. The reaction mixture was cooled over an ice bath then a solution of *N*,*N*-diisopropylethylamine (36 μL, 0.21 mmol, 2.0 equiv) in dichloromethane (2.0 mL) was added dropwise over 30 minutes. The mixture was allowed to warm to rt then stirred for 18 h. The mixture was then quenched with 1 M hydrochloric acid (5 mL), extracted with dichloromethane (3 x 5 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo*. The crude product was purified by column chromatography (25% ethyl acetate in petroleum ether)

to give **381** as a white solid (32 mg, 86 µmol, 84%). R_f = 0.18 (25% ethyl acetate in petroleum ether); M.p. 165-166 °C; $[\alpha]^{32}_D$ –3.8 (*c* 0.17, $CHCl_3$); IR (film) 2923, 1635, 1509, 1254, 1175 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 7.81-7.73 (2H, br m, Ar-H), 7.78 (2H, d, *J* 8.4, Ar-CH), 7.32 (2H, t, *J* 7.4, Ar-*H*), 7.26 (1H, t, *J* 7.2, Ar-H), 7.05 (2H, d, *J* 8.2, Ar-H), 6.91 (2H, d, *J* 8.1, Ar-H), 6.78 (2H, d, *J* 8.8, Ar-H), 5.72-5.64 (1H, br m, C*H*Ph), 3.92-3.79 (1H, br m, NC*H*H), 3.80 (3H, s, OCH_3), 3.60-3.39 (1H, br m, NCH*H*), 2.58 (1H, sextet, *J* 12.0, CHPhC*H*H), 2.32-2.18 (4H, br m, CHPhCH*H* and CH_3Ar); δ*C* (100 MHz; $CDCl_3$) 161.7 (Ar-C), 132.3 (Ar-CH), 130.9 (Ar-CH), 129.5 (Ar-CH), 128.4 (Ar-CH), 127.2 (Ar-CH), 126.9 (Ar-C), 113.8 (Ar-CH), 113.0 (Ar-CH), 62.8 (CH, seen on HSQC), 55.2 (OCH_3), 29.7 (CH_2), 20.5 (CH_3), 3 Ar-C, 1 CH_2 and 1 C=O not seen; HRMS (ESI^+) calculated for $C_{24}H_{24}N_2O_2$ $[M+Na]^+$ 395.1730; found 395.1727.



(*R*)-4-(3-([1,1'-Biphenyl]-4-yl)-2-propionylpyrazolidin-1-yl)benzonitrile (382). Cyclic hydrazine **365** (20 mg, 47 µmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2.0 mL) and stirred for 2 h. It was then concentrated *in vacuo* then propionyl chloride (12 µL, 0.14 mmol, 2.5 equiv) and dichloromethane (47 µL, 0.1 M) were added. The reaction mixture was cooled over an ice bath then a solution of *N*,*N*-diisopropylethylamine (16 µL, 94 µmol, 2.0 equiv) in dichloromethane (2 mL) was added dropwise over 30 minutes. The mixture was allowed to warm to rt then stirred for 18 h. The mixture was then quenched with 1 M hydrochloric acid (5 mL), extracted with dichloromethane (3 × 5 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo* and the crude product was purified by column chromatography (50% ethyl acetate in petroleum ether) to give **382** as a yellow oil (12 mg, 31 µmol, 66%). R_f = 0.16 (50% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ – 22.2 (*c* 0.12, $CHCl_3$). IR (film) 2925, 2220, 1675, 1603, 1504, 1175 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.56 (4H, t, *J* 7.7, Ar-H), 7.53 (2H, d, *J* 8.3, Ar-H), 7.45 (2H, t, *J* 7.6, Ar-H), 7.40-7.34 (3H, m, Ar-*H*), 7.03 (2H, d, *J* 8.4, Ar-H), 5.51 (1H, t, *J* 7.3, C*H*Ph), 4.12-4.04 (1H, br

m, NC*H*H), 3.60-3.52 (1H, m, NCH*H*), 2.67-2.52 (2H, m, CHPhC*H*H and CO_2C*H*H), 2.35-2.20 (2H, m, CHPhCH*H* and CO_2CH*H*), 1.12 (3H, t, *J* 7.4, CH_3); δ*C* (125 MHz; $CDCl_3$) 153.5 (C=O), 140.7 (Ar-C), 140.5 (Ar-C), 139.1 (Ar-C), 133.5 (Ar-CH), 128.8 (Ar-CH), 128.1 (Ar-CH), 127.4 (Ar-CH), 127.3 (Ar-CH), 127.1 (Ar-CH), 119.2 (Ar-C), 115.3 (Ar-CH), 114.1 (Ar-CH), 104.0 (CN), 61.2 (CH), 53.1 (CH_2), 33.7 (CH_2), 26.4 (CH_2), 8.6 (CH_3); HRMS (ESI^+) calculated for $C_{25}H_{23}N_3O$ $[M+Na]^+$ 404.1733; found 404.1732.

Buchwald-Hartwig Amination Screen 3 – Screen of 385•X

Initially product **384** was analysed by GCMS to determine its retention time and the relationship between peak area and concentration. The following solutions were made using dichloromethane to test this (Table 6.3).

Solution	Method	Concentration / ng mL^{-1}
Stock 1	9.6 mg **384** in 10 mL	9,600,000
Stock 2	1 mL Stock 1 in 50 mL	192,000
Cal 9	2 mL Stock 2 in 10 mL	38,400
Cal 8	1 mL Stock 2 in 10 mL	19,200
Cal 7	2 mL Cal 9 in 5 mL	15,360
Cal 6	2 mL Cal 8 in 5 mL	7,680
Cal 5	1.25 mL Cal 8 in 5 mL	4,800
Cal 4	0.5 mL Cal 9 in 5 mL	3,840
Cal 3	0.75 mL Cal 8 in 5 mL	2,880
Cal 2	0.6 mL Cal 8 in 5 mL	2,300
Cal 1	1 mL Cal 8 in 10 mL	1,920

Table 6.3 Dilutions used to develop calibration standards for **384**.

1 mL of each of these calibration solutions (Cal 1-9) was transferred to a 2 mL Agilent GCMS vial. Each vial was injected into the GCMS then the peak at a retention time of 16.8 min was integrated to give a peak area in arbitrary units, which gave Table 6.4

Cal Standard	**Concentration / ng mL^{-1}**	**Peak Area / arbitrary units**
9	38,400	1,315,842
8	19,200	824,285
7	15,360	717,993
6	7,680	340,497
5	4,800	243,299
4	3,840	167,593
3	2,880	170,035
2	2,300	131,578
1	1920	82,854

Table 6.4 Peak area data for the GCMS calibration of **384**.

When this was plotted (Figure 6.2) Cal 9 was omitted as this was clearly an outlier. This was likely due to the sample concentration being too high which saturated the UV detector on the GCMS. The remaining samples gave a strong linear relationship between peak area and concentration (R^2 = 0.9901), with a concentration of 1 ng mL^{-1} corresponding to 45 arbitrary units of peak area.

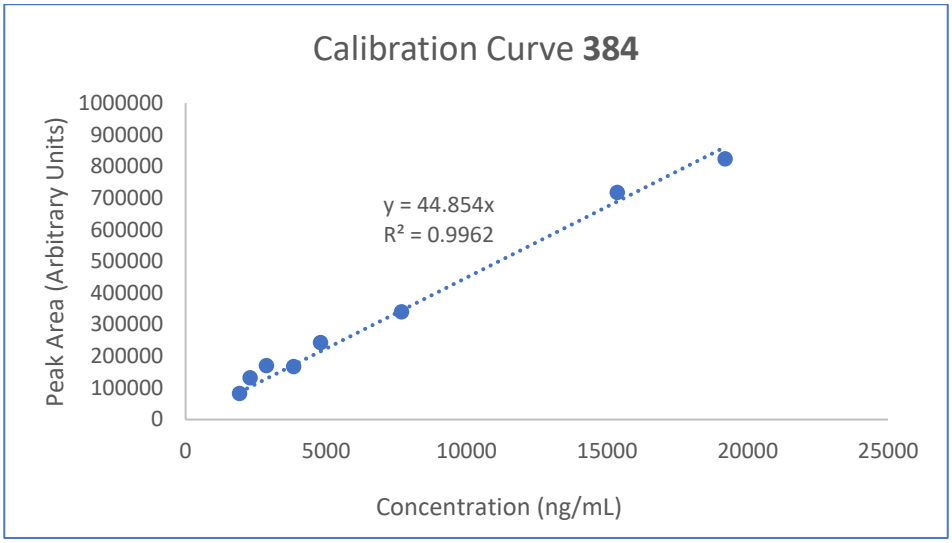
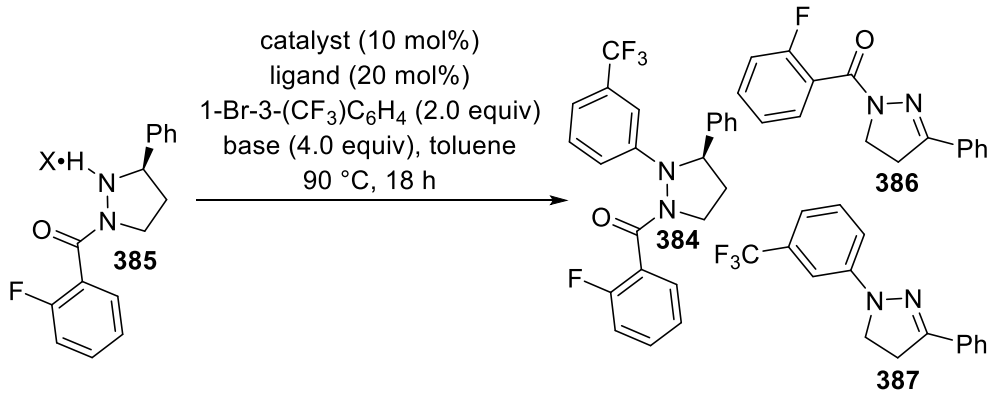


Figure 6.2 Calibration curve of **384**.



Scheme 6.9 Optimisation of the synthesis of **384**.

The reactions were performed in an aluminium heating block with 9 x 4 mL Fisher Scientific Reactivials, each with a teflon coated magnetic stirrer bar. These vials were labelled R1-R9 then the following reagents were added to each:

R1: **385•TFA** (4.2 mg, 11 µmol, 1.0 equiv), XPhos Pd(crotyl)Cl (0.8 mg, 1.1 µmol, 0.1 equiv), sodium *tert*-butoxide (4.3 mg, 44 µmol, 4.0 equiv) and toluene (1 mL).

R2: **385•TFA** (5.8 mg, 15 µmol, 1.0 equiv), XPhos Pd(crotyl)Cl (1.1 mg, 1.5 µmol, 0.1 equiv), sodium *tert*-butoxide (5.9 mg, 60 µmol, 4.0 equiv) and dioxane (1 mL).

R3: **385•TFA** (4.4 mg, 12 µmol, 1.0 equiv), XPhos Pd(crotyl)Cl (0.8 mg, 1.2 µmol, 0.1 equiv), potassium carbonate (6.6 mg, 48 µmol, 4.0 equiv) and toluene (1 mL).

R4: **385•TFA** (7.4 mg, 19 µmol, 1.0 equiv), $Pd(OAc)_2$ (0.4 mg, 1.9 µmol, 0.1 equiv), Xantphos (2.2 mg, 3.8 µmol, 0.2 equiv), sodium *tert*-butoxide (10.5 mg, 76 µmol, 4.0 equiv) and toluene (1 mL).

R5: **385•TFA** (5.9 mg, 15 µmol, 1.0 equiv), $Pd(OAc)_2$ (0.3 mg, 1.5 µmol, 0.1 equiv), Xphos (2.4 mg, 3.0 µmol, 0.2 equiv), sodium *tert*-butoxide (5.9 mg, 60 µmol, 4.0 equiv) and toluene (1 mL).

R6: **385•HCl** (3.6 mg, 12 µmol, 1.0 equiv), $Pd(OAc)_2$ (0.2 mg, 1.2 µmol, 0.1 equiv), Xantphos (1.4 mg, 2.4 µmol, 0.2 equiv), sodium *tert*-butoxide (4.7 mg, 48 µmol, 4.0 equiv) and toluene (1 mL).

R7: **385•HCl** (7.1 mg, 23 µmol, 1.0 equiv), $Pd(OAc)_2$ (0.2 mg, 2.3 µmol, 0.1 equiv), Xantphos (2.7 mg, 4.6 µmol, 0.2 equiv), sodium *tert*-butoxide (9.0 mg, 92 µmol, 4.0 equiv) and dioxane (1 mL).

R8: **385•HCl** (3.7 mg, 12 µmol, 1.0 equiv), $Pd(OAc)_2$ (0.2 mg, 1.2 µmol, 0.1 equiv), Xantphos (1.4 mg, 2.4 µmol, 0.2 equiv), potassium carbonate (6.6 mg, 48 µmol, 4.0 equiv) and toluene (1 mL).

R9: **385•HCl** (2.7 mg, 9 µmol, 1.0 equiv), $Pd(OAc)_2$ (0.2 mg, 0.9 µmol, 0.1 equiv), Xantphos (1.1 mg, 1.8 µmol, 0.2 equiv), potassium carbonate (5.0 mg, 36 µmol, 4.0 equiv) and dioxane (1 mL).

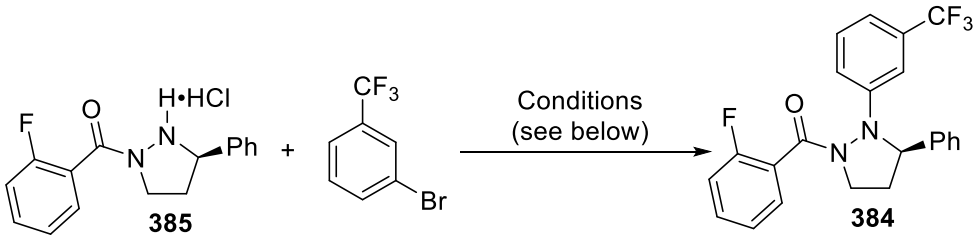
All vials were sealed with subaseals and then placed under an atmosphere of nitrogen. The reactions were heated for 20 hours at 90 °C, then the crude reaction mixture of each was filtered through a plug of cotton wool into a 5 mL volumetric flask using dichloromethane as the eluent. Each flask was made up to volume with dichloromethane and 20 µL of each solution was removed using a Hamilton syringe and transferred to a 2 mL Agilent GCMS vial. 980 µL of dichloromethane was added to each then the samples were analysed by GCMS. The peak areas of **384** were used to generate the following data (Table 6.5).

Rxn	385 / µmol	Peak Area	Conc / ng mL^{-1}	384 / mg	384 / µmol	% 385
R1	11	187,078	1,039,322	1.0	2.5	23
R2	15	78,101	433,894	0.4	1.0	7
R3	12	74,351	413,061	0.4	1.0	9
R4	19	603,309	3,351,717	3.4	8.1	42
R5	15	433,784	2,409,911	2.4	5.8	38
R6	12	517,164	2,873,133	2.9	6.9	59
R7	23	908,105	5,045,028	5.0	12.2	53
R8	12	70,578	392,100	0.4	1.0	8
R9	9	0	0	0.0	0.0	0

Table 6.5 Raw data used to calculate yield of **385**.

N.B. Impurities **386** and **387** identified in Scheme 6.9 were seen in multiple reactions and were assigned retention times. **386** was consistently seen at 14.9 min and **387** was consistently seen at 13.6 min. As these were only seen in the small scale reactions they were never isolated and fully characterised, however crude NMR data and the mass peaks seen in the GCMS strongly suggested that the structures proposed are plausible.

Buchwald-Hartwig Amination Screen 4 – Second Screen of **385•HCl**



Scheme 6.10 Buchwald-Hartwig Amination screen of **385•**HCl

The reactions were performed in an aluminium heating block with 48 x 750 µL vials, each with a teflon coated magnetic stirrer bar. These vials were arranged

in 12 columns (labelled 1-12) and 4 rows (labelled A-D). The following powders were weighed into the vials using a Mettler Toledo QX96 powder dispenser inside a glovebox.

All vials in row A: Sodium *tert*-butoxide (4.7 mg, 49 µmol, 3.0 equiv).

All vials in rows B, F: Caesium carbonate (15.9 mg, 49 µmol, 3.0 equiv).

All vials in rows C, G: Potassium carbonate (6.8 mg, 49 µmol, 3.0 equiv).

All vials in rows D, H: Potassium phosphate tribasic (10.4 mg, 49 µmol, 3.0 equiv).

All vials in column 1: [XantPhos Pd(allyl)]Cl (1.2 mg, 1.6 µmol, 0.1 equiv).

All vials in column 2: [(*R*)-BINAP Pd(allyl)]Cl (1.4 mg, 1.6 µmol, 0.1 equiv).

All vials in column 3: $Pd(dppf)Cl_2 \cdot$ Dichloromethane (1.3 mg, 1.6 µmol, 0.1 equiv).

All vials in column 4: [P(*t*Bu)$_3$] Pd(crotyl) Cl (0.7 mg, 2.0 µmol, 0.12 equiv).

All vials in column 5: [BippyPhos Pd(allyl)]OTf (1.3 mg, 1.6 µmol, 0.1 equiv)

All vials in column 6: AdBettPhos (1.3 mg, 2.0 µmol, 0.12 equiv) and palladium (II) acetate (0.5 mg, 2.2 µmol, 0.1 equiv).

All vials in column 7: [*t*BuBrettPhos Pd(allyl)]OTf (1.3 mg, 1.7 µmol, 0.1 equiv).

All vials in column 8: MorDalPhos (0.9 mg, 2.0 µmol, 0.12 equiv) and palladium (II) acetate (0.5 mg, 2.2 µmol, 0.1 equiv).

All vials in column 9: [BrettPhos Pd(crotyl)]OTf (1.4 mg, 1.7 µmol, 0.1 equiv).

All vials in column 10: [*t*BuXPhos Pd(allyl)]OTf (1.2 mg, 1.7 µmol, 0.1 equiv).

All vials in column 11: XPhos Pd(crotyl)Cl (1.1 mg, 1.6 µmol, 0.1 equiv).

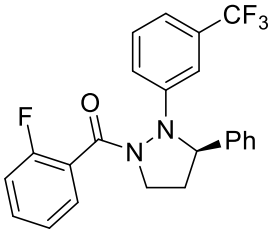
All vials in column 12: RuPhos Pd(crotyl)Cl (1.1 mg, 1.7 µmol, 0.1 equiv).

Stock Solution: (2-Fluorophenyl)-[(3*R*)-3-phenylpyrazolidin-1-yl]methanone hydrochloride (**14**) (258 mg, 0.78 mmol) and 3-bromobenzotrifluoride (265 mg, 164 µL, 1.18 mmol) in toluene (3.60 mL).

All vials were dosed with 75 µL of Stock Solution which contained (2-fluorophenyl)-[(3*R*)-3-phenylpyrazolidin-1-yl]methanone hydrochloride (**385**) (5.4 mg, 16 µmol, 1.0 equiv) and 3-bromobenzotrifluoride (5.5 mg, 34 µL, 25 µmol, 1.5 equiv).

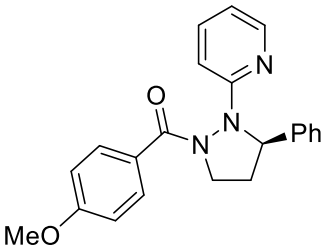
N.B. **385** was obtained by stirring **376** (1 g) in HCl/dioxane solution (10 mL) for 2 h. This solution was then concentrated in vacuo to give **385** as a pale yellow solid which was used in the screen without further purification.

The plate was sealed with a silicone and PFA mat and placed on an HEL polyblock. The plate was then heated at 90 °C for 16 h. The vials were the cooled to rt and DMSO (300 µL) was added to each using a multichannel pipette. A 5 µL aliquot was extracted from each then added to a 96-well analyical plate and diluted with DMSO (50 µL). The plate was analyzed by reverse phase LCMS (XBridge C_{18} 3.5-µm 2.1 × 35 mm Column, 1.6 mL min^{-1}, 50 °C; gradient 5:95 to 99:1 (pH 9 H_2O + 10 mM NH_4HCO_2) / MeCN over 0.7 min + 0.3 min hold). The LCMS traces were processed using in-house software and the results visualized using Spotfire software to give Figure 3.3.

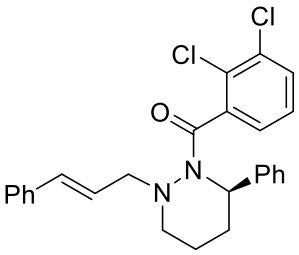


(*R*)-(2-Fluorophenyl)(3-phenyl-2-(3-(trifluoromethyl)phenyl)pyrazolidin-1-yl)methanone (384). cyclic hydrazine **376** (26 mg, 70 µmol, 1.0 equiv) was dissolved in 4M HCl/dioxane solution (2.0 mL) and stirred for 2 h at rt. It was then concentrated *in vacuo*. Pd-180 (3 mg, 4 µmol, 0.05 equiv), caesium carbonate (68 mg, 0.21 mmol, 3.0 equiv), 3-bromobenzotrifluoride (15 µL, 0.11 mmol, 1.5 equiv) and toluene (70 µL) were added and the reaction was stirred at 90 °C for 20 h. The reaction mixture was then quenched with saturated ammonium chloride solution (5 mL), extracted with dichloromethane (3 x 5 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo* and the crude product was purified by column chromatography (15% ethyl acetate in petroleum ether) to give **384** as a colourless oil (21 mg, 54 µmol, 77%). R_f = 0.15 (15% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ – 8.5 (*c* 0.14, $CHCl_3$); Enantiomeric excess (94% *ee*) was determined by HPLC analysis (25 °C). [Chiralpak IA column 2-propanol/hexane = 1/99; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 33.9 min; t_R 37.8 min; IR (film) 2925, 1659, 1491, 1382, 1211 cm^{-1}; δ*H* (500 MHz; d6-DMSO at 373 K) 7.60-7.03 (13H, m, Ar-H), 5.04 (1H, t, *J* 5.5, C*H*Ph), 4.09-3.87

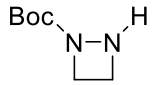
(1H, br m, NC*H*H), 3.65 (1H, dd, *J* 17.3, 8.9, NCH*H*), 2.68-2.58 (1H, br m, CHPhC*H*H), 2.34-2.22 (1H, br m, CHPhCH*H*); δ*C* (125 MHz, d6-DMSO at 373 K) 159.7 (C=O), 157.8 (Ar-C), 145.7 (Ar-CH), 132.2 (Ar-CH), 130.5 (q, *J* 31.3, Ar-C), 130.5 (Ar-CH), 129.0 (Ar-CH), 127.9 (Ar-CH), 126.8 (Ar-CH), 124.6 (q, *J* 271, CF_3), 124.5 (d, *J* 15, Ar-C), 116.2 (d, *J* 23, Ar-CH), 2 CH_2, 1 CH and 4 Ar-CH not seen; δ*F* (276 MHz; d6-DMSO) -61.1 (minor), -61.4 (CF_3), -114.7 (minor), -115.1 (Ar-CF); HRMS (ESI^+) calculated for $F_4C_{23}H_{18}N_2O$ $[M+Na]^+$ 437.1247; found 437.1248.



(*R*)-(4-Methoxyphenyl)(3-phenyl-2-(pyridin-2-yl)pyrazolidin-1-yl)methanone (389). cyclic hydrazine **373** (25 mg, 65 µmol, 1.0 equiv) was dissolved in 4M HCl/dioxane solution (2.0 mL) and stirred for 2 h at rt. It was then concentrated *in vacuo*. Pd-180 (3 mg, 3 µmol, 0.05 equiv), caesium carbonate (64 mg, 0.20 mmol, 3.0 equiv), 2-bromopyridine (9 µL, 0.10 mmol, 1.5 equiv) and toluene (65 µL) were added and the reaction was stirred at 90 °C for 20 h. The reaction mixture was then quenched with saturated ammonium chloride solution (5 mL), extracted with dichloromethane (3 x 5 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo* and the crude product was purified by column chromatography (33% ethyl acetate in petroleum ether) to give gave **389** as a colourless oil (19 mg, 52 µmol, 80%). R_f = 0.13 (33% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ + 9.2 (*c* 0.23, dichloromethane). IR (film) 2932, 1651, 1597, 1461, 1432, 1258, 1173 cm^{-1}; δ*H* (400 MHz; $CDCl_3$) 8.32 (1H, s, Ar-CH), 7.60 (1H, t, *J* 7.3, Ar-H), 7.53-6.87 (9H, m, Ar-H), 6.69 (1H, s, Ar-H), 5.88 (1H, t, *J* 7.5, C*H*Ph), 4.70-3.39 (1H, br m, NC*H*H), 3.76 (3H, s, CH_3), 3.52-3.49 (1H, br m, NCH*H*), 2.53-2.31 (2H, br m, $CHPhCH_2$); δ*C* (100 MHz; $CDCl_3$) 161.5 (C=O), 148.4 (Ar-C), 138.2 (Ar-C), 130.3 (Ar-CH), 128.4 (Ar-CH), 127.2 (Ar-CH), 126.7 (Ar-CH), 117.5 (Ar-CH), 113.0 (Ar-CH), 109.1 (Ar-CH), 66.1 (CH), 55.2 (CH_3), 44.7 (CH_2), 2 Ar-C, 2 Ar-CH and 1 CH_2 not seen; HRMS (ESI^+) calculated for $C_{22}H_{21}N_3O_2$ $[M+H]^+$ 360.1712; found 360.1712.

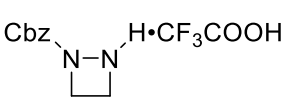


(*R*)-(2-Cinnamyl-6-phenyltetrahydropyridazin-1(*2H*)-yl)(2,3-dichlorophenyl)methanone (392). Cyclic hydrazine **440** (100 mg, 0.26 mmol, 1.0 equiv) was dissolved in 4 M HCl/dioxane solution (2.0 mL) and stirred for 2 h. It was then concentrated *in vacuo* and 2,3-dichlorobenzoyl chloride (139 mg, 0.66 mmol, 2.5 equiv) and dichloromethane (100 µL and 2 mL) were added. The reaction mixture was cooled over an ice bath then a solution of *N*,*N*-diisopropylethylamine (93 µL, 0.53 mmol, 2.0 equiv) in dichloromethane (2 mL) was added dropwise over 30 min. The mixture was allowed to warm to rt then stirred for 18 h. The mixture was then quenched with 1.0 M hydrochloric acid (5.0 mL), extracted with dichloromethane (3 × 5.0 mL) and dried over magnesium sulphate. It was then concentrated *in vacuo*. and the crude product was purified by column chromatography (10% ethyl acetate in petroleum ether) to give **XX** as a colourless oil (95 mg, 0.21 mmol, 80%). R_f = 0.10 (10% ethyl acetate in petroleum ether); $[\alpha]^{32}_D$ + 2.1 (*c* 0.61, $CHCl_3$). IR (film) 2934, 2866, 1642, 1414, 970 cm^{-1}; δ*H* (500 MHz; $CDCl_3$) 7.63 (2H, d, *J* 7.4, Ar-H), 7.47 (1H, d, *J* 7.2, Ar-H), 7.44 (2H, t, *J* 7.6, Ar-H), 7.35 (1H, t, *J* 7.3, Ar-H), 7.27-7.18 (5H, m, Ar-H), 7.09 (2H, d, *J* 7.3, Ar-H), 6.09 (1H, d, *J* 3.5, C=CH), 5.76 (1H, d, *J* 15.9, C=CH), 5.43-5.33 (1H, br m, C*H*Ph), 3.14 (1H, dd, *J* 12.9, 7.6, NC*H*H), 2.90 (1H, d, *J* 11.5, NC*H*HCH=CH), 2.69 (1H, d, *J* 11.3, NCH*H*), 2.27-2.15 (2H, m, CHPhC*H*H and NCH*H*CH=CH), 1.69-1.50 (2H, m, CHPhCH*H* and CH_2CHHCH_2), 1.52-1.46 (1H, m, CH_2CHHCH_2); δ*C* (125 MHz; $CDCl_3$) 169.9 (C=O), 140.8 (Ar-C), 136.5 (Ar-C), 133.1 (Ar-C), 131.9 (C=CH) 129.6 (Ar-CH), 128.7 (Ar-CH), 128.5 (Ar-CH), 128.3 (Ar-C), 127.5 (Ar-CH), 127.4 (Ar-CH), 127.3 (Ar-CH), 127.3 (Ar-CH), 126.1 (Ar-CH), 125.5 (Ar-CH), 57.8 (CH_2), 48.4 (CH), 40.8 (CH_2), 24.4 (CH_2), 14.0 (CH_2), 1 Ar-C not seen; HRMS (ESI^+) calculated for $C_{26}H_{24}N_2O^{35}Cl_2$ $[M+Na]^+$ 473.1158; found 473.1151.



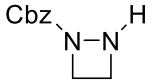
***tert*-Butyl 1,2-diazetidine-1-carboxylate (398) 198** (50 mg, 0.17 mmol, 1.0 equiv.) and Pd/C (5 mg, 10 wt%) were stirred in ethyl acetate (5 mL) under an H_2 atmosphere (1 atm.) for 1 h, at which point TLC showed complete consumption of starting material. The solution was filtered through a plug of Celite and silica using ethyl acetate as the eluent and the resulting colourless solution was concentrated in vacuo to give a colourless oil (26 mg, 0.16 mmol 96%), which required no further purification; R_f = 0.11 (40% ethyl acetate in petroleum ether); IR (Film) 3263, 2976, 2931, 2902, 1698, 1365, 1147; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 5.41 (1H, br s, NH), 4.33 (2H, t, *J* 7.9, NHC*H*$_2$), 3.77 (2H, br s, NBocCH_2), 1.50 (9H, s, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ*C* 160.1 (C=O), 81.0 (C), 51.9 (CH_2), 41.4 (CH_2), 29.3 (CH_3); HRMS (ESI^+) calculated for $C_7H_{14}N_2O_2$ $(M+Na)^+$: 181.0947; found: 181.0948.

202 (100 mg, 0.32 mmol, 1.0 equiv.) and activated magnesium turnings (78 mg, 3.2 mmol, 10 equiv.) were stirred in methanol (3 mL) for 5 h. Brine (10 mL) and saturated ammonium chloride (10 mL) were then added and the crude mixture was extracted with dichloromethane (3 x 10 mL), dried over $MgSO_4$ and then concentrated *in vacuo* to give a colourless oil (50 mg, 0.31 mmol, 98%) which required no further purification; Data is consistent with that reported above.

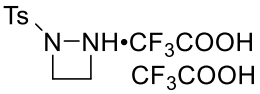


TFA salt of benzyl 1,2-diazetidine-1-carboxylate (399•TFA**) 198** (100 mg, 0.34 mmol, 1.0 equiv.) was dissolved in dichloromethane (5 mL). Trifluoroacetic acid (0.26 mL, 3.4 mmol, 10.0 equiv.) was added dropwise and the resulting pale-yellow solution was stirred for monitored by TLC and was complete after 3 h. the solution was concentrated *in vacuo* to give a yellow oil. This gave the desired product as a yellow oil (66 mg, 0.34 mmol, 100%) which required no further purification; IR (film) 1740, 1667, 1394, 1310, 1136; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 7.79 (2H, s, NH_2), 7.27 (5H, m, Ar-CH), 5.05 (2H, s, CH_2Ph), 4.35 (2H, t, *J* 7.9, NCH_2), 4.11 (2H, t, *J* 7.9, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ*C* 157.0 (C=O), 129.0 (Ar-CH), 128.8 (Ar-C), 128.7 (Ar-CH), 128.5 (Ar-CH), 69.6 (CH_2), 51.21

(CH_2), 42.6 (CH_2), 1 C=O and CF_3 not seen; HRMS (ES^+) calculated for $C_{10}H_{12}N_2O_2$ $(M+Na)^+$: 215.0791; found: 215.0792.



Benzyl 1,2-diazetidine-1-carboxylate and Benzyl 1,2-diazetidine (399) 399•TFA (66 mg, 0.34 mmol, 1.0 equiv.) was dissolved in dichloromethane (10 mL) and then washed with saturated sodium hydrogen carbonate (10 mL) and water (10 mL). The aqueous layer was then washed with dichloromethane and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give **399** as an orange oil which required no further purification (53 mg, 0.28 mmol 82%); R_f = 0.11 (40% ethyl acetate in petroleum ether); IR (film) 3245, 2902, 1701, 1497, 1305, 1142; ^{1}H NMR (300 MHz, $CDCl_3$) δ*H* 7.36 (5H, m, Ar-CH), 5.19 (2H, s, CH_2Ph), 4.43 (2H t, *J* 8.0, NCH_2), 3.82 (2H, br s, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ*C* 135.5 (C=O), 128.8 (Ar-C), 128.6 (Ar-CH), 128.5 (Ar-CH), 128.3 (Ar-CH), 68.2 (CH_2), 51.0 (CH_2), 41.0 (CH_2); HRMS (ES^+) calculated for $C_{10}H_{12}N_2O_2$ $(M+Na)^+$: 215.0791; found: 215.0781.

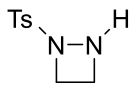


TFA salt of 1-tosyl-1,2-diazetidine (401•2TFA**) 203** (0.50 g, 1.6 mmol, 1.0 equiv.), trifluoroacetic acid (1.23 mL, 16 mmol, 10.0 equiv.) and dichloromethane (10 mL) were combined to give a pale yellow solution that was stirred at room temperature for 24 h. The solution was then concentrated *in vacuo* to give a yellow crystalline solid. This was purified by recrystallisation from hot toluene (approx. 15 mL) to give a white crystalline solid (281 mg, 0.64 mmol, 40%); M.p. 79-81 °C; IR (film) 2963, 2954, 2915, 2849, 1773, 1732, 1664, 1370; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 7.92 (2H, d, *J* 8.2, Ar-CH), 7.43 (2H, d, *J* 8.0, Ar-CH), 4.46 (2H, s, NH_2), 4.15 (2H, t, *J* 8.2, NCH_2), 3.60 (2H, t, *J* 8.2, NCH_2), 2.51 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ*C* 158.6 (C=O), 145.1 (Ar-C), 130.2 (Ar-CH), 129.6 (Ar-CH), 129.1 (Ar-C), 51.2 (CH_2), 41.4 (CH_2), 21.7

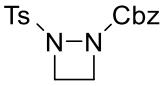
(CH_3), 2 x CF_3 not seen; HRMS (ES^+) calculated for $C_9H_{12}N_2O_2S$ $(M+Na)^+$: 235.0512; found: 235.0510.

Single crystals of **401•**2TFA were grown from dichloromethane/hexane. A suitable crystal was selected and mounted on a glass fibre with Fromblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a duel source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL refinement package using Least Squares minimisation.

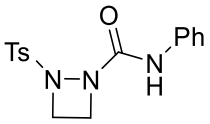
Crystal Data for **401•2TFA** (*M* =440.32 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 13.07690(10) Å, *b* = 24.3100(2) Å, *c* = 11.26310(10) Å, β = 91.5510(10)°, *V* = 3579.22(5) $Å^3$, *Z* = 8, *T* = 150(2) K, μ(CuKα) = 2.527 mm^{-1}, *Dcalc* = 1.634 g/cm^3, 82190 reflections measured (6.762° ≤ 2Θ ≤ 148.27°), 7207 unique (R_{int} = 0.0945, R_{sigma} = 0.0330) which were used in all calculations. The final R_1 was 0.0518 (I > 2σ(I)) and wR_2 was 0.1347 (all data).



1-Tosyl-1,2-diazetidine (401) 401•2TFA (25 mg, 80 μmol) was dissolved in dichloromethane (10 mL) and then washed with saturated sodium hydrogen carbonate (10 mL). The organic layer was dried over $MgSO_4$ and then concentrated *in vacuo* to give **401** as a colourless oil (17 mg, quant.); R_f = 0.13 (50% ethyl acetate in petroleum ether); IR (film) 3242, 2990, 1745, 1695, 1530, 1159; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 7.92 (2H, d, *J* 8.2, Ar-H), 7.43 (2H, d, *J* 8.0, Ar-H), 6.40 (1H, br s, NH), 3.75 (2H, t, *J* 8.2, NCH_2), 3.45 (2H, t, *J* 8.2, NCH_2) 2.51 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ_c 145.7 (C), 130.3 (CH), 129.4 (CH), 129.0 (C), 51.5 (CH_2), 41.3 (CH_2), 21.7 (CH_3); MS (ES^+) *m/z* = 447 ($[2M+Na]^+$, 62); HRMS (ES^+) *calculated* for $C_9H_{12}N_2O_2SNa$ $(M+Na)^+$: 235.0512; found: 235.0509.

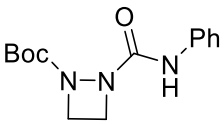


Benzyl 2-tosyl-1,2-diazetidine-1-carboxylate (402) To a solution of sodium hydroxide (12 mg, 0.30 mmol, 2.0 equiv) in water (5 mL), dichloromethane (5 mL) was added. **401**•2TFA (50 mg, 0.15 mmol, 1.0 equiv) was added and the mixture was cooled over an ice bath. Benzyl chloroformate (22 μL, 0.15 mmol, 1.0 equiv) was added. The mixture was left to warm to rt and stirred for 20 h. After this time, the organic layer was collected and washed with water (5 mL) and 20% citric acid solution (5 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give a colourless oil (20 mg, 57 μmol 38%) which required no further purification; R_f 0.15 (15% EtOAc in petroleum ether); IR (film) 2979, 2928, 1714, 1330, 1305, 1137; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 7.78 (2H, d, *J* 8.2, Ar-H), 7.28 (7H, m, Ar-H), 5.08 (2H, s, CH_2Ph), 4.03 (2H, t, *J* 8.3, CH_2), 3.90 (2H, t, *J* 8.0, CH_2), 2.38 (3H, s, CH_3), ^{13}C NMR (125 MHz, $CDCl_3$) δ*C* 160.1 (C=O), 145.3 (Ar-C), 135.3 (Ar-C), 130.1 (Ar-CH), 129.9 (Ar-C), 129.6 (Ar-CH), 128.5 (Ar-CH), 128.3 (Ar-CH), 128.0 (Ar-CH), 68.4 (CH_2), 49.4 (CH_2), 47.9 (CH_2), 21.8 (CH_3); HRMS (ESI$^+$) calculated for $C_{17}H_{18}N_2O_4S$ $(M+Na)^+$: 369.0879; found: 369.0879.



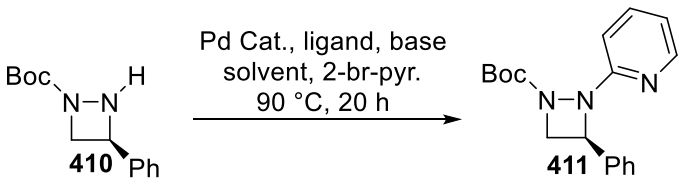
***N*-Phenyl-2-tosyl-1,2-diazetidine-1-carboxamide (404) 401** (80 mg, 0.38 mmol, 1.0 equiv), dichloromethane (5 mL) and phenylisocyanate (40 μL, 0.38 mmol, 1.0 equiv) were combined and stirred at room temperature for 24 h. The solution was then concentrated *in vacuo* to give a yellow solid (124 mg, 0.37 mmol, 98%), which required no further purification; R_f 0.27 (33% EtOAc in petroleum ether); M.p. 141-142 °C; IR (film) 3347, 2950, 1697, 1596, 1540, 1345; ^{1}H NMR (600 MHz, d6-DMSO at 353 K) δ*H* 8.44 (1 H, s, NH), 7.94 (2H, d, *J* 8.2, Ar-H), 7.59 (2H, d, *J* 8.2, Ar-H), 7.49 (2H, d, *J* 7.9, Ar-H), 7.35 (2H, t, *J* 7.9, Ar-H), 7.10 (1H, t, *J* 7.4, Ar-H), 4.09 (2H, t, *J* 8.1, NCH_2), 3.79 (2H, t, *J* 8.1, NCH_2), 2.50 (3H, s, CH_3); ^{13}C NMR (125 MHz, d6-DMSO) δ*C* 158.5 (C=O), 146.4 (Ar-C), 138.4 (Ar-C), 130.6 (Ar-CH), 130.5 (Ar-CH), 129.4 (Ar-CH), 128.2 (Ar-C), 123.9

(Ar-CH), 119.4 (Ar-CH), 49.0 (CH_2), 48.8 (CH_2), 21.7 (CH_3); HRMS (ES^+) *calculated* for $C_{16}H_{17}N_3O_3S$ $(M+Na)^+$: 354.0883; found: 354.0876.



***tert*-Butyl 2-(phenylcarbamoyl)-1,2-diazetidine-1-carboxylate (405) 398** (100 mg, 0.32 mmol, 1.0 equiv), activated magnesium turnings (39 mg, 1.60 mmol, 5.0 equiv) and methanol (5 mL) were stirred at rt for 2 h. This was then quenched with saturated ammonium chloride solution (5 mL) and extracted with dichloromethane (3 x 5 mL). The organic was dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. Dichloromethane (5 mL) and phenylisocyanate (38 μL, 0.35 mmol, 1.1 equiv) were combined and stirred at rt for 24 h. The solution was then concentrated *in vacuo* to give a colourless oil. This was purified by column chromatography (25% EtOAc in petroleum ether) to give the desired product as a white solid (53 mg, 0.19 mmol, 60%); R_f 0.38 (25% EtOAc in petroleum ether); M.p. 125-126 °C; IR (film) 3394, 2982, 1712, 1670, 1536, 1290, 1143; ^{1}H NMR (500 MHz, $CDCl_3$) δ*H* 8.62 (1 H, s, NH), 7.48 (2H, d, *J* 7.7, Ar-H), 7.33 (2H, t, *J* 7.9, Ar-H), 7.08 (1H, t, *J* 7.4, Ar-H), 4.22 (4H, s, 2 x CH_2), 1.58 (9H, s, $(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ*C* 161.4 (C=O), 161.3 (C=O), 138.2 (Ar-C), 129.0 (Ar-CH), 123.4 (Ar-CH), 119.2 (Ar-CH), 83.8 (C) 48.5 (CH_2), 46.4 (CH_2), 28.2 (CH_3); HRMS (ES^+) *calculated* for $C_{14}H_{19}N_3O_3$ $(M+Na)^+$: 300.1319; found: 300.1322.

<u>Buchwald-Hartwig Amination Screen 5 – Screen of 410</u>

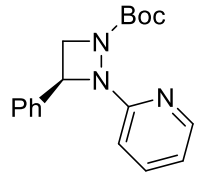


Scheme 6.11 Buchwald-Hartwig Amination screen of **410**.

Authentic examples of **410**, **411** and 2-bromopyridine were run on the GCMS and were found to have retention times of 9.7 min, 11.0 min and 7.5 min respectively.

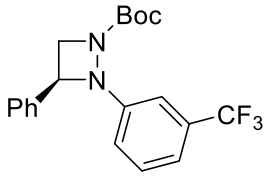
The reactions were performed in an aluminium heating block with 9 x 4 mL Fisher Scientific Reactivials, each with a teflon coated magnetic stirrer bar. These vials were labelled R1-R9 then the following reagents were added to each:
R1: **410** (5.0 mg, 13 µmol, 1.0 equiv), palladium acetate (0.3 mg, 1.3 µmol, 0.1 equiv), Xantphos (1.5 mg, 2.6 µmol, 0.2 equiv), sodium *tert*-butoxide (2.5 mg, 26 µmol, 2.0 equiv), toluene (1 mL).
R2: **410** (5.0 mg, 13 µmol, 1.0 equiv), palladium acetate (0.3 mg, 1.3 µmol, 0.1 equiv), Xantphos (1.5 mg, 2.6 µmol, 0.2 equiv), cesium carbonate (8.5 mg, 26 µmol, 2.0 equiv), toluene (1 mL).
R3: **410** (5.0 mg, 13 µmol, 1.0 equiv), palladium acetate (0.3 mg, 1.3 µmol, 0.1 equiv), Xantphos (1.5 mg, 2.6 µmol, 0.2 equiv), sodium *tert*-butoxide (2.5 mg, 26 µmol, 2.0 equiv), dioxane (1 mL).
R4: **410** (5.0 mg, 13 µmol, 1.0 equiv), palladium dibenzylacetone (1.2 mg, 1.3 µmol, 0.1 equiv), Xantphos (1.5 mg, 2.6 µmol, 0.2 equiv), sodium *tert*-butoxide (2.5 mg, 26 µmol, 2.0 equiv), toluene (1 mL).
R5: **410** (5.0 mg, 13 µmol, 1.0 equiv), palladium acetate (0.3 mg, 1.3 µmol, 0.1 equiv), *tert*-butyl-Xphos (1.1 mg, 2.6 µmol, 0.2 equiv), sodium *tert*-butoxide (2.5 mg, 26 µmol, 2.0 equiv), toluene (1 mL).
R6: **410** (5.0 mg, 13 µmol, 1.0 equiv), palladium acetate (0.3 mg, 1.3 µmol, 0.1 equiv), cyJonphos (0.9 mg, 2.6 µmol, 0.2 equiv), sodium *tert*-butoxide (2.5 mg, 26 µmol, 2.0 equiv), toluene (1 mL).
R7: **410** (5.0 mg, 13 µmol, 1.0 equiv), palladium acetate (0.3 mg, 1.3 µmol, 0.1 equiv), 1,1′-Ferrocenediyl-bis(diphenylphosphine) (1.4 mg, 2.6 µmol, 0.2 equiv), sodium *tert*-butoxide (2.5 mg, 26 µmol, 2.0 equiv), toluene (1 mL).
R8: **410** (5.0 mg, 13 µmol, 1.0 equiv), palladium dibenzylacetone (1.2 mg, 1.3 µmol, 0.1 equiv), 1,1′-Ferrocenediyl-bis(diphenylphosphine) (1.4 mg, 2.6 µmol, 0.2 equiv), cesium carbonate (8.5 mg, 26 µmol, 2.0 equiv), toluene (1 mL).
R9: **410** (5.0 mg, 13 µmol, 1.0 equiv), palladium dibenzylacetone (1.2 mg, 1.3 µmol, 0.1 equiv), 1,1′-Ferrocenediyl-bis(diphenylphosphine) (1.4 mg, 2.6 µmol, 0.2 equiv), cesium carbonate (8.5 mg, 26 µmol, 2.0 equiv), dioxane (1 mL).
All vials were sealed with subaseals and then placed under an atmosphere of nitrogen. The reactions were heated for 20 hours at 90 °C, then the crude reaction

mixture of each was filtered through a plug of cotton wool into a vial using dichloromethane as the eluent. Each vial had approximately 5 mL of dichloromethane added. 20 µL of each solution was removed using a Hamilton syringe and transferred to a 2 mL Agilent GCMS vial. 980 µL of dichloromethane was added to each then the samples were analysed by GCMS. As the screen was not designed to be quantitative, GCMS traces were simply analysed for the presence or absence of peaks with retention times corresponding to **410** and **411**. This analysis was used to generate Table 3.3.



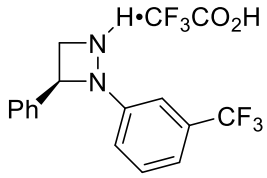
***tert*-Butyl (*S*)-3-phenyl-2-(pyridin-2-yl)-1,2-diazetidine-1-carboxylate 411** cyclic hydrazine **212** (100 mg, 0.26 mmol, 1.0 equiv), activated magnesium turnings (31 mg, 1.29 mmol, 5.0 equiv) and methanol (2.6 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extrcts were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. palladium acetate (6 mg, 26 µmol, 0.1 equiv), Xantphos (30 mg, 51 µmol, 0.2 equiv), sodium *tert*-butoxide (49 mg, 0.51 mmol, 2.0 equiv), 2-bromopyridine (49 µL, 0.51 mmol, 2.0 equiv) and toluene (2.6 mL, 0.1 M) were combined and stirred at 90 °C for 18 h. The reaction was quenched with saturated ammonium chloride (5 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over magnesium sulphate and concentrated in vacuo to give a brown oil. This was purified by column chromatography (10% ethyl acetate and 1% triethylamine in petroleum ether) to yield **411** as a pale yellow solid (33 mg, 0.11 mmol, 41%). R_f = 0.29 (10% EtOAc and 1% triethylamine in petroleum ether); M.p. 68-69 °C; $[\alpha]^{32}_D$ + 8.20 (c 0.02, $CHCl_3$). IR (film) 3234, 2925 1714, 1591, 1368, 1072 cm^{-1}; δH (500 MHz; $CDCl_3$); 8.16 (1H, d, *J* 4.6, Ar-CH), 7.55-7.41 (1H, m, Ar-CH), 7.48 (1H, d, Ar-CH), 7.48 (2H, d, *J* 7.5, Ar-CH), 7.34 (2H, t, *J* 7.7, Ar-CH), 7.25 (1H, t, *J* 7.4, Ar-CH), 6.95 (1H, d, *J* 8.3, Ar-CH), 6.79 (1H, dd, *J* 6.8 and 5.4, Ar-CH), 5.33 (1H, dd, *J* 8.4 and 7.0, CHPh), 4.57 (1H, t, *J* 8.5,

NCHH) 4.10 (1H, dd, *J* 7.8, 7.0, NCHH), 1.47 (9H, s, $C(CH_3)_3$); δC (125 MHz; $CDCl_3$) 164.4 (C=O), 161.3 (Ar-C), 147.7 (Ar-CH), 140.4 (Ar-C), 137.3 (Ar-CH), 128.8 (Ar-CH), 127.9 (Ar-CH), 126.2 (Ar-CH), 117.2 (Ar-CH), 109.8 (Ar-CH), 82.3 (C), 64.3 (CH), 57.3 (CH_2), 28.3 (CH_3); HRMS (ESI^+) calculated for $C_{18}H_{21}N_3O_2$ $[M+Na]^+$ 334.1525; found 335.1524.

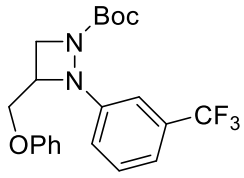


***tert*-Butyl (*S*)-3-phenyl-2-(3-(trifluoromethyl)phenyl)-1,2-diazetidine-1-carboxylate (413).** Cyclic hydrazine **212** (100 mg, 0.26 mmol, 1.0 equiv), magnesium turnings (31 mg, 1.29 mmol, 5.0 equiv) and methanol (2.6 mL, 0.1 M) were combined and stirred (800 rpm) at room temperature for 2 hours. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. Palladium acetate (6.0 mg, 26 µmol, 0.1 equiv), Xantphos (30 mg, 51 µmol, 0.2 equiv), sodium *tert*-butoxide (49 mg, 0.51 mmol, 2.0 equiv), 3-trifluoromethyl-bromobenzene (71 µL, 0.51 mmol, 2.0 equiv) and toluene (2.6 mL, 0.1 M) were combined and stirred at 90 °C for 18 h. The reaction was quenched with saturated ammonium chloride (5 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over magnesium sulphate and concentrated *in vacuo* to give a brown oil. This was purified by column chromatography (25% ethyl acetate in petroleum ether) to yield **413** as an orange oil (35 mg, 90 µmol, 35%). R_f = 0.78 (25% EtOAc/petroleum ether); $[\alpha]^{24}_D$ + 4.6 (*c* 0.23, $CHCl_3$); IR (film) 2978, 1715, 1327, 1120, 1028 cm^{-1}; δ*H* (500 MHz; $CDCl_3$); 7.56 (2H, d, *J* 7.3, Ar-H), 7.48 (2H, t, *J* 7.5, Ar-H), 7.42 (1H, d, *J* 7.2, Ar-H), 7.33 (1H, t, *J* 7.9, Ar-H), 7.22 (1H, d, *J* 7.7, Ar-H), 7.15 (1H, s, Ar-H), 6.94 (1H, d, *J* 8.6, Ar-H), 4.94 (1H, t, *J* 8.4, CHPh), 4.58 (1H, t, *J* 8.5, NC*H*H) 4.10 (1H, t, *J* 7.6, NCH*H*), 1.56 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 161.1 (C=O), 153.6 (Ar-C), 139.1 (Ar-C), 130.9 (q, *J* 31.3, Ar-C), 129.1 (Ar-CH), 129.0 (Ar-CH), 128.7 (Ar-CH), 126.7 (Ar-CH), 124.1 (q, *J* 271.3, CF_3), 118.4 (q, *J* 3.8, Ar-CH), 117.4 (Ar-CH), 111.3

(q, *J* 5.0, Ar-CH), 82.5 (C), 67.7 (CH), 56.8 (CH_2), 28.2 (CH_3); δ*F* (376 MHz; $CDCl_3$) -62.8 (CF_3); HRMS (ESI^+) calculated for $C_{20}H_{21}N_2O_2F_3$ $[M+Na]^+$ 401.1447; found 401.1450.

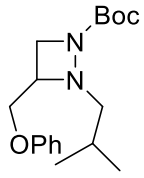


(*S*)-4-Phenyl-1-(3-trifluoromethyl)phenyl-1,2-diazetidine trifluoroacetic acid (414•TFA**).** Cyclic hydrazine **414** (14 mg, 38 µmol, 1.0 equiv), trifluoroacetic acid (30 µL, 0.38 mmol, 10.0 equiv) and dichloromethane (1.0 mL) were stirred at rt for 2 h then concentrated *in vacuo* to yield **414•**TFA as an orange oil (13 mg, 33 µmol, 88%). $[\alpha]^{24}_D$ – 4.8 (*c* 0.36, $CHCl_3$); IR (film) 2920, 2852 1759, 1460, 1232, 1032 cm^{-1}; δ*H* (500 MHz; $CDCl_3$); 7.46-7.37 (6H, m, Ar-H), 7.20 (1H, d, *J* 7.6, Ar-H), 7.05 (1H, s, Ar-H), 6.99 (1H, d, *J* 8.1, Ar-H), 5.69 (1H, t, *J* 8.0, CHPh), 4.20 (1H, t, *J* 8.3, NC*H*H), 3.73 (1H, t, *J* 8.3, NCH*H*), δ*C* (125 MHz; $CDCl_3$) 146.4 (Ar-C), 137.1 (Ar-C), 130.0 (Ar-CH), 129.4 (Ar-CH), 129.1 (Ar-CH), 125.7 (Ar-CH), 118.2 (q, *J* 3.8, Ar-CH), 116.4 (Ar-CH), 109.7 (q, *J* 2.5, Ar-CH), 74.5 (CH), 53.9 (CH_2), 28.2 (CH_3), 1 C=O, 2 CF_3 and 1 Ar-C not seen; δ*F* (376 MHz; $CDCl_3$) –62.9 (CF_3), –70.8 and –70.9 (1:1 rotamer, CF_3CO_2H); HRMS (ESI^+) calculated for $C_{15}H_{13}N_2F_3$ $[M+Na]^+$ 301.0929; found 301.0930.



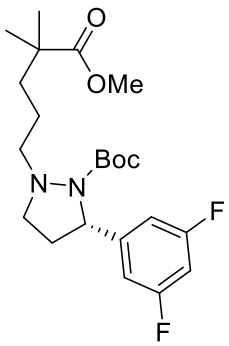
***tert*-Butyl (*rac*)-3-(phenoxymethyl)-2-(3-(trifluoromethyl)phenyl)-1,2-diazetidine-1-carboxylate (415).** Cyclic hydrazine *rac*-**218** (100 mg, 0.24 mmol, 1.0 equiv), magnesium turnings (29 mg, 1.19 mmol, 5.0 equiv) and methanol (5 mL) were combined and stirred (800 rpm) at room temperature for 2 h. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. Palladium acetate (4.5 mg, 20 µmol, 0.1 equiv), Xantphos (29 mg, 50 µmol, 0.2 equiv), sodium *tert*-butoxide (48 mg, 0.5 mmol, 2.0 equiv), 3-

trifluoromethyl-bromobenzene (70 µL, 0.5 mmol, 2.0 equiv) and toluene (5 mL) were combined and stirred at 90 °C for 18 h. The reaction was quenched with saturated ammonium chloride (5 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil. This was purified by column chromatography (15% ethyl acetate in petroleum ether) to yield **415** as an orange oil (12 mg, 28 µmol, 12%). M.p. 108-109 °C; R_f = 0.49 (15% EtOAc/petroleum ether); IR (film) 2918, 1737, 1709, 1334, 1076, cm^{-1}; δ*H* (500 MHz; $CDCl_3$); 7.42-7.38 (2H, m, Ar-H), 7.34-7.30 (2H, m, Ar-H), 7.25-7.20 (2H, m, Ar-H), 7.00 (1H, tt, *J* 7.5, 1.0, Ar-H), 6.96 (2H, ddd, *J* 4.5, 3.3, 1.8, Ar-H), 4.45-4.39 (2H, m, C*H*HOPh and NC*H*H), 4.36-4.30 (1H, m, NCH), 4.26 (1H, dd, *J* 9.8, 3.8, CH*H*OPh), 4.21 (1H, dd, *J* 8.3, 6.3, NCH*H*), 1.52 (9H, s, $C(CH_3)_3$); δ*C* (125 MHz; $CDCl_3$) 160.7 (C=O), 158.2 (Ar-C), 153.0 (Ar-C), 139.1 (Ar-C), 130.9 (q, *J* 31.3, Ar-C), 129.6 (Ar-CH), 129.0 (Ar-CH), 121.5 (Ar-CH), 118.6 (q, *J* 3.8, Ar-CH), 117.8 (Ar-CH), 114.5 (Ar-CH), 111.8 (q, *J* 3.8, Ar-CH), 82.5 (C), 69.4 (CH_2), 64.0 (CH), 50.7 (CH_2), 28.2 (CH_3), CF_3 not seen; δ*F* (376 MHz; $CDCl_3$) -62.7 (CF_3); HRMS (ESI^+) calculated for $C_{21}H_{23}N_2O_3F_3$ $[M+Na]^+$ 431.1553; found 431.1549.



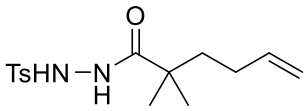
***tert*-Butyl (*rac*)-2-isobutyl-3-(phenoxymethyl)-1,2-diazetidine-1-carboxylate (416).** Cyclic hydrazine *rac*-**218** (100 mg, 0.24 mmol, 1.0 equiv), magnesium turnings (29 mg, 1.19 mmol, 5.0 equiv) and methanol (5 mL) were combined and stirred (800 rpm) at room temperature for 2 h. The solution was quenched with saturated ammonium chloride solution (5 mL), then extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. Isobutyraldehyde (109 µL, 1.19 mmol, 5.0 equiv), sodium triacetoxyborohydride (252 mg, 1.19 mmol, 5.0 equiv), and dichloromethane (5 mL) were combined and stirred at rt for 24 h. The reaction was quenched with 1 M NaOH solution (5 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. This was purified by

column chromatography (10% ethyl acetate in petroleum ether) to yield **416** as a colourless oil (29 mg, 91 µmol, 38%). R_f = 0.47 (10% EtOAc/petroleum ether); IR (film) 2973, 1681, 1495, 1388, 1242, cm^{-1}; δ*H* (500 MHz; $CDCl_3$); 7.30-7.26 (2H, m, Ar-H), 6.98-6.94 (1H, m, Ar-H), 6.89-6.86 (2H, m, Ar-H), 4.26 (1H, t, *J* 8.4, NC*H*H), 4.09 (2H, qd, *J* 9.7, 6.0, C*H*HOPh and CH*H*OPh), 3.92 (1H, t, *J* 7.5, NCH*H*), 3.57 (1H, quintet, *J* 6.5, NCH), 2.94 (1H, dd, *J* 11.5, 8.5, C*H*HCH(CH_3)$_2$), 2.67 (1H, dd, *J* 11.5, 6.0, CH*H*CH(CH_3)$_2$), 1.87-1.78 (1H, m, C*H*(CH_3)$_2$), 1.47 (9H, s, C(CH_3)$_3$), 0.96 (6H, d, *J* 6.7, (CH_3)$_2$); δ*C* (125 MHz; $CDCl_3$) 160.7 (C=O), 158.5 (Ar-C), 129.5 (Ar-CH), 121.1 (Ar-CH), 114.5 (Ar-CH), 80.9 (C), 70.3 (CH_2), 69.7 (CH_2), 60.6 (CH), 50.8 (CH_2), 28.2 (CH_3), 25.7 (CH), 21.4 (CH_3), 20.9 (CH_3); HRMS (ESI^+) calculated for $C_{18}H_{28}N_2O_3$ $[M+Na]^+$ 343.1992; found 343.1986.

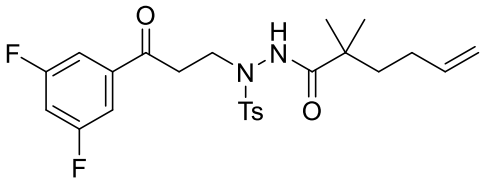


***tert*-Butyl (*S*)-5-(3,5-difluorophenyl)-2-(5-methoxy-4,4-dimethyl-5-oxopentyl)pyrazolidine-1-carboxylate (340). 313** (200 mg, 0.46 mmol, 1.0 equiv), activated magnesium turnings (55 mg, 2.28 mmol, 5.0 equiv), and methanol (10 mL) were stirred at rt for 2 h. The solution was quenched with saturated ammonium chloride solution (5 mL), extracted with dichloromethane (3 x 5 mL) and dried over $MgSO_4$. The solution was concentrated *in vacuo* to give a colourless oil. To this was added **338** (364 mg, 2.30 mmol, 5.0 equiv), sodium triacetoxyborohydride (487 mg, 2.30 mmol, 5.0 equiv) and dichloromethane (5 mL, 0.1 M) and the mixture was stirred at rt. After 20 hours it was quenched with 2 M sodium hydroxide solution (10 mL), extracted with dichloromethane (3 X 10 mL), dried over $MgSO_4$ and concentrated in vacuo to give a brown oil. The crude material was purified by column chromatography (10% ethyl acetate in petroleum ether) to give **340** as colourless oil (118 mg, 0.28 mmol, 61%). R_f = 0.38 (50% EtOAc in petroleum ether); $[\alpha]^{24}_D$ –8.8 (*c* 0.27, $CHCl_3$); IR (film) 2955, 1737, 1457, 1317, 1056, cm^{-1}; δ*H* (500 MHz; $CDCl_3$ at 323 K); *N.B.* This compound was obtained as a mixture of 2 rotamers, only the peaks of the major

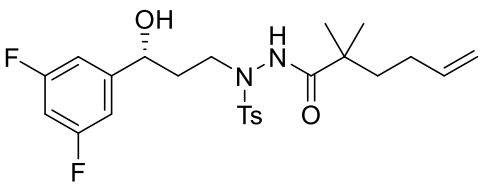
rotamer are reported. 6.77 (1H, dd, *J* 6.5, Ar-H), 6.67 (1H, t, *J* 8.8, Ar-H), 4.94 (1H, t, *J* 8.3, CHAr), 3.66 (3H, s, CO_2CH_3), 3.41 (1H, dd, *J* 11.0, 6.5, NC*H*H), 3.15 (1H, td, *J* 11.3, 6.0, NCH*H*), 3.10-3.00 (1H, m, NCH*H*), 2.69-2.63 (1H, m, NCH*H*), 2.50 (1H, ddd, *J* 11.2, 6.8, 2.6, ArCHC*H*H), 2.12 (1H, ddd, *J* 10.9, 8.5, 2.6, ArCHCH*H*), 1.65-1.63 (2H, m, CH_2), 1.57-1.53 (2H, m, CH_2), 1.27 (9H, s, $(CH_3)_3$), 1.21 (6H, s, $(CH_3)_2$); δ*C* (125 MHz; $CDCl_3$ at 323 K) 178.2 (C=O), 162.3 (d, *J* 10.0, Ar-CF), 148.2 (C=O), 108.5 (t, *J* 18.1, Ar-H), 102.1 (t, *J* 21.3, Ar-CH), 80.7 (C), 62.7 (CH), 58.7 (CH_2), 51.5 (CH_3), 38.1 (CH_2), 34.5 (CH_2), 35.4 (CH_2), 29.6 (CH_2), 28.2 (CH_3), 25.1 (CH_3), 25.0 (CH_3), 24.1 (C), Ar-C not seen; δ*F* (376 MHz; $CDCl_3$) -109.7 (Ar-CF); HRMS (ESI^+) calculated for $C_{22}H_{32}N_2O_4F_2$ $[M+Na]^+$ 449.2222; found 449.2222.



***N*'-(2,2-Dimethylhex-5-enoyl)-4-methylbenzenesulfonohydrazide (343).** *para*-Toluenesulfonyl hydrazide(1.94 g, 10.1 mmol, 0.9 equiv), dichloromethane (20 mL) and triethylamine (2.10 mL, 15.1 mmol, 1.3 equiv) were stirred at 0 °C, then **342**[111] (1.49 g, 11.6 mmol, 1.0 equiv) in dichloromethane (30 mL) was added dropwise. The solution was allowed to warm to rt and stirred for 18 h. The solution was then quenched with saturated sodium hydrogen carbonate solution (10 mL), extracted with dichloromethane (3 x 10 mL), dried over magnesium sulphate and concentrated *in vacuo*. The crude material was purified by column chromatography to give **343** as a white solid (914 mg, 3.1 mmol, 30%). R_f = 0.52 (33% EtOAc in petroleum ether); M.p. 123-124 °C; IR (film) 3341, 2973, 1681, 1494, 1164, cm^{-1}; δ*H* (500 MHz; $CDCl_3$); 7.82 (2H, d, *J* 8.3, Ar-H), 7.45 (1H, d, *J* 6.5, NH), 7.31 (2H, d, *J* 8.2, Ar-H), 5.65 (1H, ddt, *J* 19.5, 9.7, 6.5, *H*C=CHH), 4.93-4.89 (2H, m, HC=C*HH*), 2.43 (3H, s, Ar-CH_3), 1.63 (2H, m, CH_2), 1.42 (2H, m, CH_2), 1.06 (6H, s, 2 x CH_3); δ*C* (125 MHz; $CDCl_3$) 175.9 (C=O), 145.0 (Ar-C), 137.9 (H*C*=CH_2), 132.9 (Ar-C), 129.5 (Ar-CH), 129.0 (Ar-CH), 114.7 (HC=*C*H_2), 39.7 (CH_2), 28.7 (CH_2), 24.5 (CH_3), 21.7 (CH_3); HRMS (ESI^+) calculated for $C_{15}H_{22}N_2O_3S$ $[M+Na]^+$ 333.1243; found 333.1248.

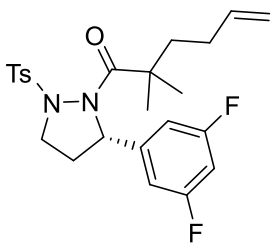


_N_-(3-(3,5-difluorophenyl)-3-oxopropyl)-N'-(2,2-dimethylhex-5-enoyl)-4-methylbenzenesulfonohydrazide (345). **343** (495 mg, 2.42 mmol, 1.0 equiv), **344** (751 mg, 2.42 mmol, 1.0 equiv), potassium carbonate (368 mg, 2.66 mmol) and acetonitrile (50 mL) were stirred at rt for 24 h. The solution was then quenched with water (25 mL), extracted with dichloromethane (3 x 25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (15% ethyl acetate in petroleum ether) to give **345** as a white solid (975 mg, 2.03 mmol, 84%). R_f = 0.16 (15% EtOAc in petroleum ether); M.p. 108-109 °C; IR (film) 2932, 1686, 1594, 1474, 1311, 1045 cm^{-1}; δ*H* (500 MHz; $CDCl_3$); 7.80 (2H, d, *J* 8.3, Ar-H), 7.59 (1 H, s, Ar-H) 7.47 (2H, dd, *J* 7.6, 2.0, Ar-H), 7.32 (2H, d, *J* 8.2, Ar-H), 7.05 (1H, tt, *J* 8.4, 2.3, *H*C=CHH), 5.71 (1H, ddt, *J* 16.8, 10.2, 6.5, C=C*H*H), 5.00-4.89 (1H, m, HC=CH*H*), 3.97 (2H, t, *J* 6.3, NCH_2), 3.37 (2H, t, *J* 6.3, $COCH_2$), 2.43 (3H, s, Ar-CH_3), 1.85-1.79 (2H, m, HHC=CHC*H*$_2$), 1.54-1.46 (2H, m, $C(CH_3)_2C$*H*$_2$), 1.12 (6H, s, 2 x CH_3); δ*C* (125 MHz; $CDCl_3$) 195.7 (C=O), 175.7 (C=O), 163.1 (dd, *J* 261.3, 11.3, Ar-CF), 144.7 (Ar-C), 139.2 (t, *J* 7.5, Ar-C), 138.0 (H*C*=CH_2), 134.3 (Ar-C), 129.6 (Ar-CH), 128.5 (Ar-CH), 114.6 (HC=*C*H_2), 111.1 (dd, *J* 20.0, 6.3, Ar-CH), 108.8 (t, *J* 25.0, Ar-CH), 45.8 (CH_2), 41.7 (*C*$(CH_3)_2$), 39.9 (CH_2), 38.1 (CH_2), 28.9 (CH_2), 25.0 (CH_3), 21.7 (CH_3); δ*F* (376 MHz; $CDCl_3$) -107.7 (Ar-CF); HRMS (ESI^+) calculated for $C_{24}H_{28}N_2O_4SF_2$ $[M+H]^+$ 479.1811; found 479.1809.



(*R*)-*N*-(3-(3,5-difluorophenyl)-3-hydroxypropyl)-*N*'-(2,2-dimethylhex-5-enoyl)-4-methylbenzenesulfonohydrazide (441). **345** (760 mg, 1.59 mmol, 1.0 equiv), (*R*,*R*)-**247** (11 mg, 16 µmol, 0.01 equiv), 5 : 2 formic acid : triethylamine solution (1.6 mL, 1.0 M) and

dichloromethane (6.4 mL, 0.25 M) were stirred at 24 °C for 24 hours. The solution was concentrated *in vacuo* to give a red oil. The crude material was purified by column chromatography to give **441** as a white solid (759 mg, 1.58 mmol, 99%). R_f = 0.31 (33% EtOAc in petroleum ether); M.p. 91-92 °C; $[\alpha]^{24}_D$ + 25.3 (*c* 0.18, $CHCl_3$); Enantiomeric excess (98% *ee*) was determined by HPLC analysis (25 °C). [Chiralcel OD-H column 2-propanol/hexane = 3/97; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 32.6 min; t_R 38.7 min; IR (film) 3320, 2969, 2924 1684, 1624, 1317, 1116 cm^{-1}; δ*H* (500 MHz; $CDCl_3$); 7.86 (2H, d, *J* 8.3, Ar-H), 7.39-7.33 (3H, m, Ar-H), 6.97-6.91 (2H, m, Ar-H), 6.70 (1H, tt, *J* 8.9, 2.3, *H*C=CHH), 5.72 (1H, ddt, *J* 16.8, 10.2, 6.5, C=C*H*H), 5.12-5.03 (1H, m, C*H*OH), 4.99-4.93 (1H, m, HC=CH*H*), 3.77-3.67 (1H, m, NC*H*H), 3.65-3.59 (1H, m, NCH*H*), 2.45 (3H, s, Ar-CH_3), 2.00-1.93 (1H, m, CHOHC*H*H), 1.83-1.78 (3H, m, H_2C=CHC*H*$_2$, CHOHCH*H*), 1.56-1.49 (2H, m, C(CH_3)$_2$C*H*$_2$), 1.14 (3H, s, CH_3), 1.13 (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 176.5 (C=O), 163.1 (dd, *J* 246.2, 11.3, Ar-CF), 149.0 (t, *J* 8.8, Ar-C), 145.1 (Ar-C), 137.8 (H*C*=CH_2), 133.5 (Ar-C), 129.7 (Ar-H), 128.7 (Ar-H), 114.8 (HC=*C*H_2), 108.5 (dd, *J* 20.0, 5.0, Ar-H), 102.4 (t, *J* 25.0, Ar-H), 70.8 (CH), 47.8 (CH_2), 41.8 (*C*(CH_3)$_2$), 39.9 (CH_2), 36.3 (CH_2), 28.9 (CH_2), 25.2 (CH_3), 25.1 (CH_3), 21.7 (CH_3); δ*F* (376 MHz; $CDCl_3$) -109.5 (Ar-CF); HRMS (ESI^+) calculated for $C_{24}H_{30}N_2O_4SF_2$ $[M+Na]^+$ 503.1787; found 503.1786.



(*S*)-1-(5-(3,5-Difluorophenyl)-2-tosylpyrazolidin-1-yl)-2,2-dimethylhex-5-en-1-one (346). 441 (759 mg, 1.58 mmol, 1.0 equiv), triphenylphosphine (1.04 g, 3.95 mmol, 2.5 equiv), diethylazodicarboxylate (0.62 mL, 2.5 equiv) and tetrahydrofuran (158 mL, 0.01 M) were stirred at rt for 24 hours. The solution was concentrated *in vacuo* to give a yellow oil. The crude material was purified by column chromatography to give **346** as an off white solid (453 mg, 0.98 mmol, 62%). R_f = 0.08 (10% EtOAc in petroleum ether); M.p. 82-83 °C; $[\alpha]^{24}_D$ –80.0 (*c* 0.19, $CHCl_3$); Enantiomeric excess (95% *ee*) was determined by HPLC analysis (25 °C).

[Chiralcel OD-H column 2-propanol/hexane = 2/98; flow rate = 1.0 mL/min; detection wavelength = 254 nm] t_R 16.3 min; t_R 30.9 min; IR (film) 3322, 2972, 2925 1686, 1642, 1626, 1366, 1203 cm^{-1}; δ*H* (500 MHz; $CDCl_3$); 7.81 (2H, d, *J* 8.2, Ar-H), 7.32 (2H, d, *J* 8.1, Ar-H), 6.88-6.81 (2H, m, Ar-H), 6.75 (1H, tt, *J* 8.9, 2.3, *H*C=CHH), 5.75-5.63 (2H, m, C=CH_2), 4.91-4.87 (1H, m, C*H*Ar), 4.00 (1H, ddd, *J* 13.2, 7.6, 2.5, NC*H*H), 3.16 (1H, m, NCH*H*), 2.49-2.39 (4H, m, Ar-CH_3, ArCHC*H*H), 2.11-2.03 (1H, m, ArCHCH*H*), 1.93-1.77 (2H, m, H_2C=CHC*H*H, $C(CH_3)_2$C*H*H), 1.55-1.49 (1H, m, H_2C=CHCH*H*), 1.43 (1H, ddd, *J* 13.5, 11.5, 5.3, $C(CH_3)_2$CH*H*), 1.08(4) (3H, s, CH_3), 1.08(1) (3H, s, CH_3); δ*C* (125 MHz; $CDCl_3$) 163.1 (dd, *J* 247.5, 11.3, Ar-CF), 159.5 (C=O), 143.5 (t, *J* 8.8, Ar-C), 144.1 (Ar-C), 137.6 (H*C*=CH_2), 132.4 (Ar-C), 129.2 (Ar-H), 129.0 (Ar-H), 114.3 (HC=*C*H_2), 108.3 (dd, *J* 20.0, 5.0, Ar-CH), 103.5 (t, *J* 25.0, Ar-CH), 78.6 (CH), 49.5 (CH_2), 40.8 (*C*$(CH_3)_2$), 39.5 (CH_2), 35.4 (CH_2), 29.0 (CH_2), 26.0 (CH_3), 25.7 (CH_3), 21.6 (CH_3); δ*F* (376 MHz; $CDCl_3$) -107.1 (Ar-CF); HRMS (ESI^+) calculated for $C_{24}H_{28}N_2O_3SF_2$ $[M+Na]^+$ 485.1681; found 485.1687.

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